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The American Journal of Medicine

Vol. XII MARCH, 1952 No. 3

Editorial

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Clinical Studies

Treatment of H. Influenzae Meningitis with Aureomycin and Chloramphenicol. Experience in Thirty Consecutive Cases

Emanuel B. Schoenbach, Harrison C. Spencer and Jacques Monnier 263

The results of treatment of thirty children with H. influenzae type b meningitis is described. Of these, eighteen received aureomycin and sulfadiazine; twelve received chloromycetin. The general results in this dread disease were good, those with chloromycetin striking.

Diagnosis and Immediate Prognosis of Japanese B Encephalitis. Observations Based on More than 200 Patients with Detailed Analysis of 65 Serologically Confirmed Cases

Lt. Col. Robert B. Dickerson, Maj. Joseph R. Newton and Capt. James E. Hansen 277

This excellent study of a large group of cases of Japanese B encephalitis contracted in Korea throws much light upon the clinical characteristics of the disease, one of the acute viral encephalitides. Relevant laboratory findings also clarify the picture. A disappointing point made is the failure of immunization to give adequate protection.

Aureomycin in the Treatment of Systemic North American Blastomycosis

Leon V. McVay, Jr. and David S. Carroll 289

This is an interesting account of the cutaneous and systemic forms of North American blastomycosis, a disease which may well be more widespread than is appreciated. The authors were impressed with the therapeutic effects of large and prolonged dosage of aureomycin in two cases of systemic blastomycosis, ordinarily of very grave prognosis. Further trial would seem to be indicated.

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Sprague, R. G.: Cortisone and ACTH, Am. J. Med. *10*:567, 1951.

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The American Journal of Medicine

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Tuberculous Pericarditis. Its Treatment with Streptomycin and Some Observations on the Natural History of the Disease

THEODORE M. MYERS AND MORTON HAMBURGER 302

"Clinically primary" tuberculous pericarditis has a serious prognosis and it is therefore of interest that the authors were able to arrest the lesion in three cases by administration of streptomycin. Remarks on the course of the disease in nine more untreated cases of tuberculous pericarditis lend added interest to this report.

Effects of Mercurial Diuresis in Patients with Ascites Due to Cirrhosis

JAMES G. HILTON 311

The effect of mercurial diuretics in cirrhosis, particularly in the presence of marked ascites, can be markedly potentiated by ammonium chloride, as is well known. However, urinary excretion of the excess chloride involves loss of potassium, which may result in clinically significant hypokalemia requiring potassium replacement.

Clinical Observations on a New Oral Diuretic 1-Propyl-3-Ethyl-6-Aminouracil and Preliminary Studies on 1-Allyl-3-Ethyl-6-Aminouracil

A. KATTUS, T. M. ARRINGTON AND E. V. NEWMAN 319

This work reflects the efforts now being made to develop an orally effective diuretic of low toxicity. The preparations described represent encouraging progress in this direction, the sodium and water diuresis produced being comparable in many cases with the effects of parenteral mercurial diuretics.

Review

Electrokymography. I. The Ventricular Electrokymogram

SIMON DACK AND DAVID H. PALEY 331

This excellent correlative review of the application of electrokymography to the study of ventricular border motion begins with an analysis of normal findings, emphasizing contributions to better delineation of the various phases of mechanical systole and diastole. The authors then proceed to detection of impaired myocardial action in pathologic states, notably myocardial infarction, hypertensive heart disease and constrictive pericarditis.

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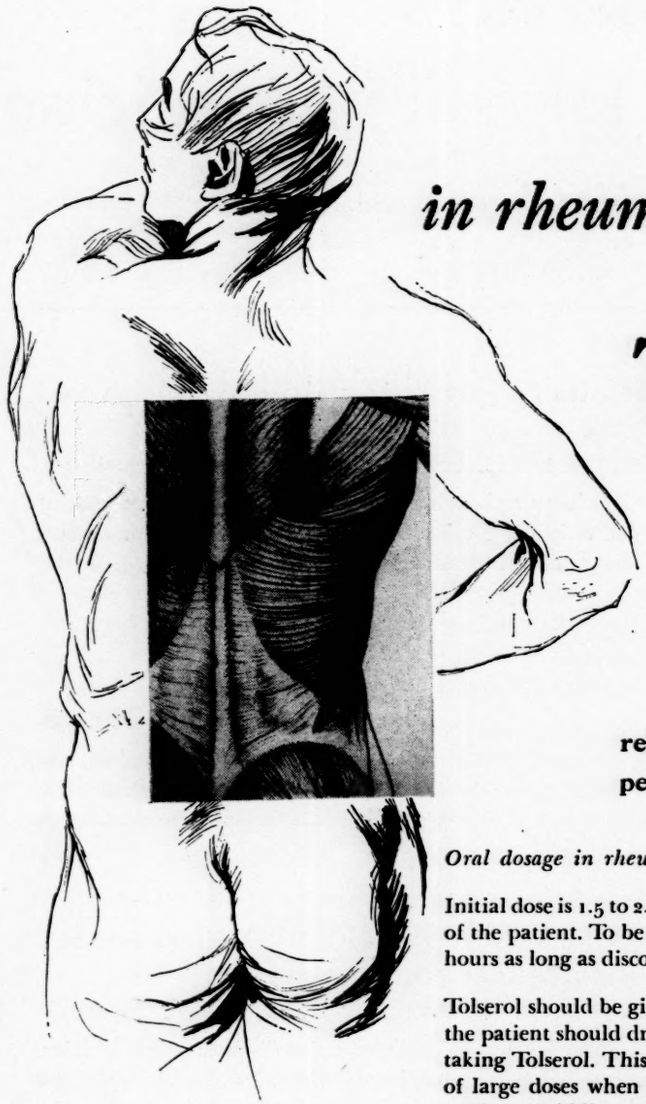

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Seminars on Congenital Heart Disease

Cardiac Catheterization in the Study of Congenital Cardiovascular Anomalies. An Evaluation . . . . . AARON HIMMELSTEIN AND ANDRE COURNAND 349

This paper from Dr. Cournand's laboratory looks back upon the accomplishments of cardiac catheterization in the diagnosis of congenital cardiovascular anomalies and makes a critical evaluation of the kind of general and specific information provided, the value of the method, its pitfalls and its hazards. The authors discuss in greater detail the four basic patterns found which cover all but the very rare anomalies.

Conference on Therapy

Low Cholesterol Diet in the Treatment of Atherosclerosis 357

Conferences on Therapy (Cornell University Medical College)—This is a lively conference dealing with a current and controversial subject, the place of dietary restriction in the prophylaxis and management of atherosclerosis. The discussion brings out no conclusive evidence, since none has yet been forthcoming, nor does it lead to any firm position in the matter, but the reader will gain perspective and insight.

Clinico-pathologic Conference

Polycystic Disease of the Kidneys with Renal Insufficiency 366

Clinico-pathologic Conference (Washington University School of Medicine)—This case gave opportunity for discussion of polycystic disease of the kidneys in both its morphologic and clinical aspects and led also to a concise but informative analysis of the biochemical and clinical characteristics of uremia. The whole makes a very worth while exercise.

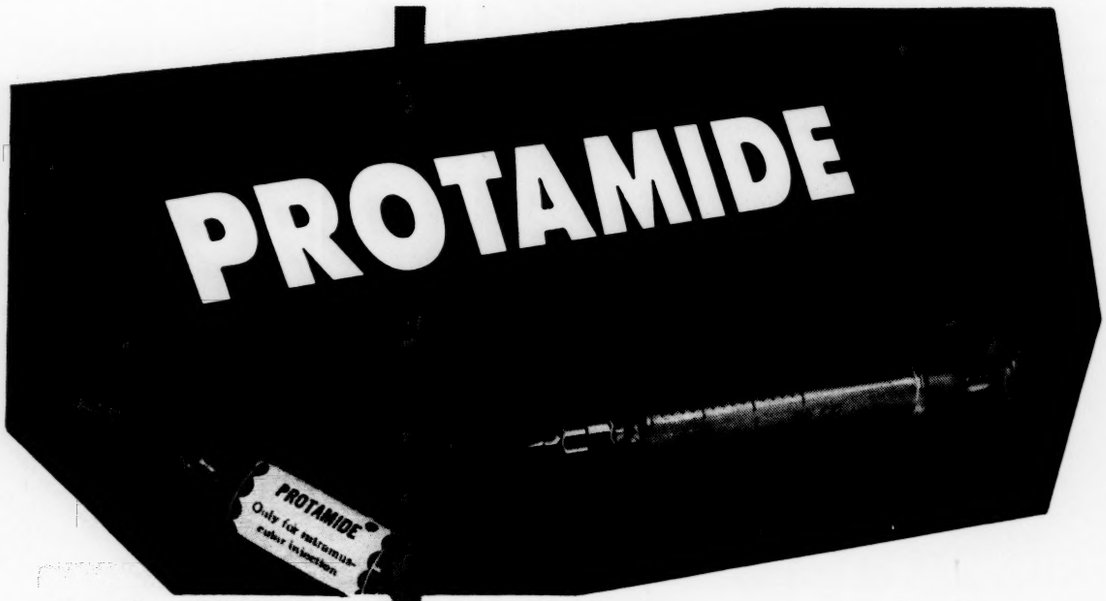
Case Report

Treatment of Unresolved Pneumonia with Streptokinase and Streptodornase JOSEPH J. MUENSTER, I. J. FLANCE AND BERNARD SWEENEY 376

Endobronchial instillation of streptokinase and streptodornase was tried in a case of D. pneumoniae pneumonitis with delayed resolution. The response was good; no significant side reactions were noted.

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.



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1. *Lehman, Arnold J.; Chase, Harold F.; Yonkman, F. F.; Urologic & Cut. Rev. 43: 378 (Aug.) 1944.*

2. *Lehrer, H. W.; Lehrer, D. R.; Lehrer, H. G.; Ohio State Medical J., P. 44 (Jan.) 1951.*

3. *Costello, Russell T.; Urologic & Cut. Rev. 51:260 (May) 1947.*

4. *Marsh, W. C.; U. S. Armed Forces Med. J. 1:1045 (Sept.) 1950.*

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CASE 43

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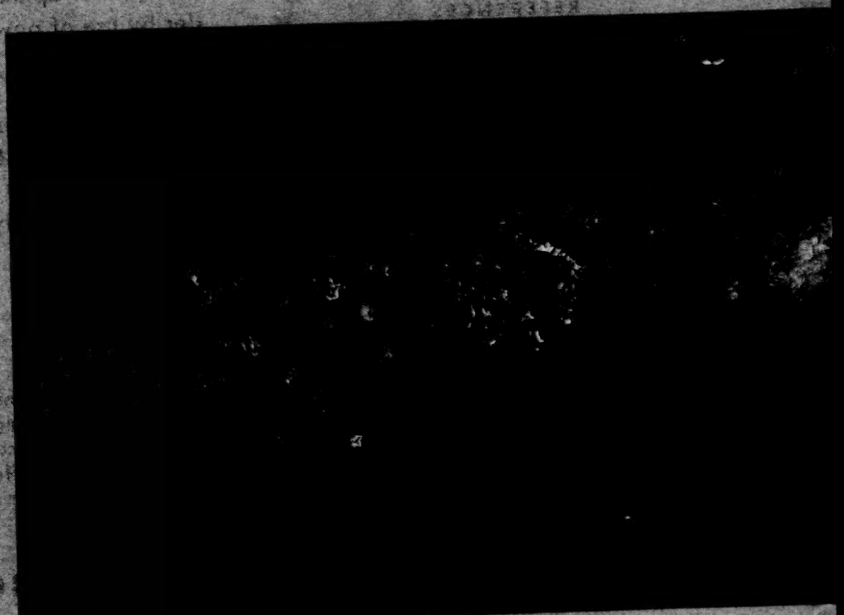

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REFERENCES

(1) Reiser, H. G., Patton, R., and Roettig, L. C.: Arch. Surg. 63: 568-575, 1951; (2) Reiser, H. G., Roettig, L. C., and Curtis, G. M.: Tryptar Debridement of Fibrinopurulent Empyema. Philadelphia, W. B. Saunders Co., 1950; (3) Reiser, H. G.: Personal Communication.

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*McLean, E. B.: Ped. 7:136, 1951

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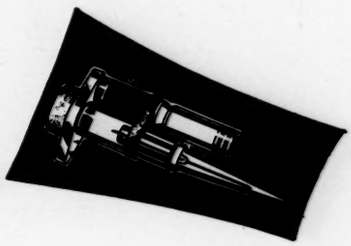

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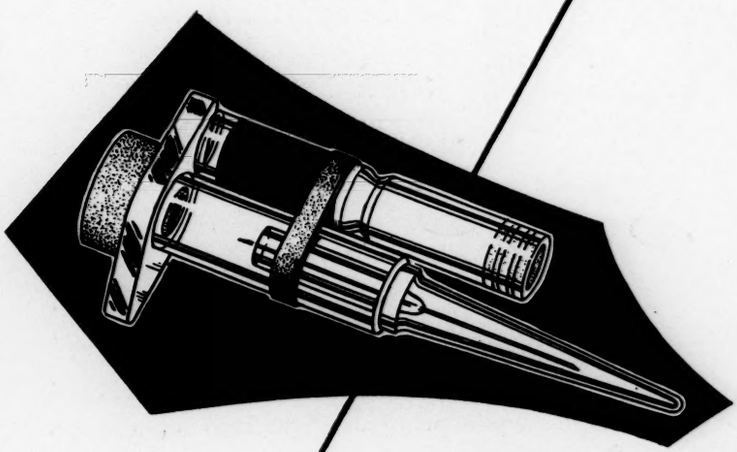

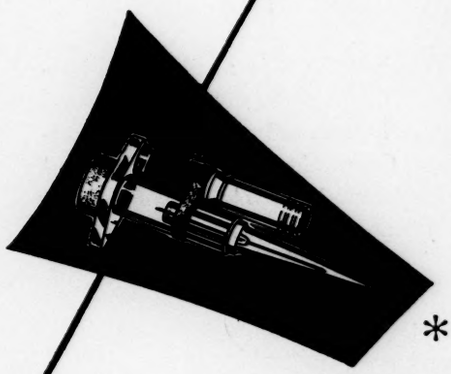

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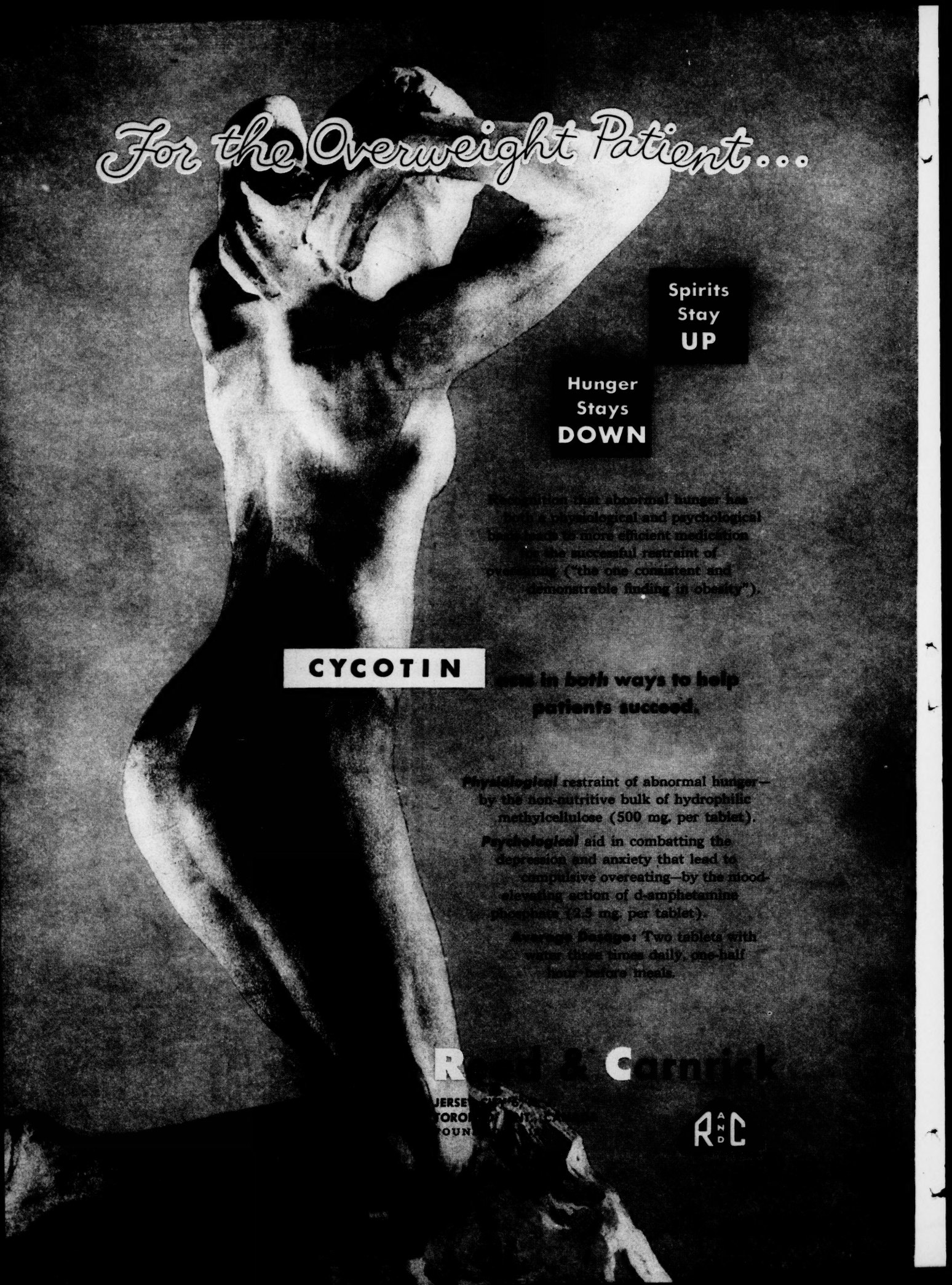
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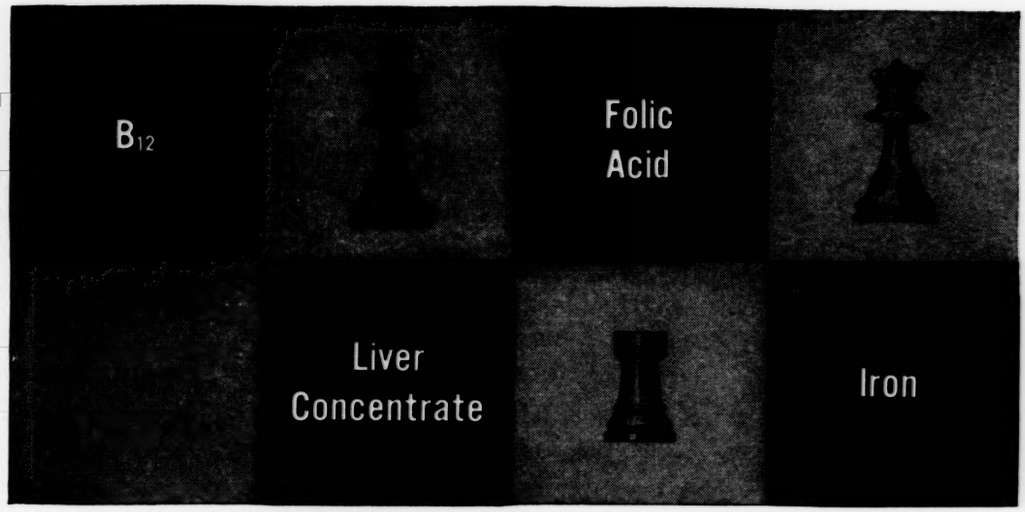

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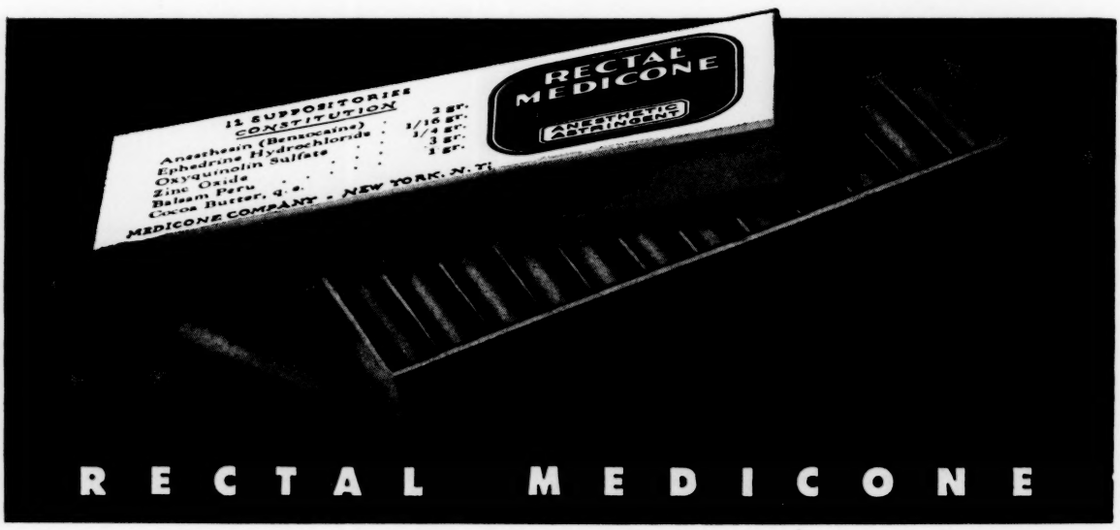

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1. Bull. Rheum. Dis. 1:9, 1951.
2. Am. J. M. Sci. 222:243, 1951.

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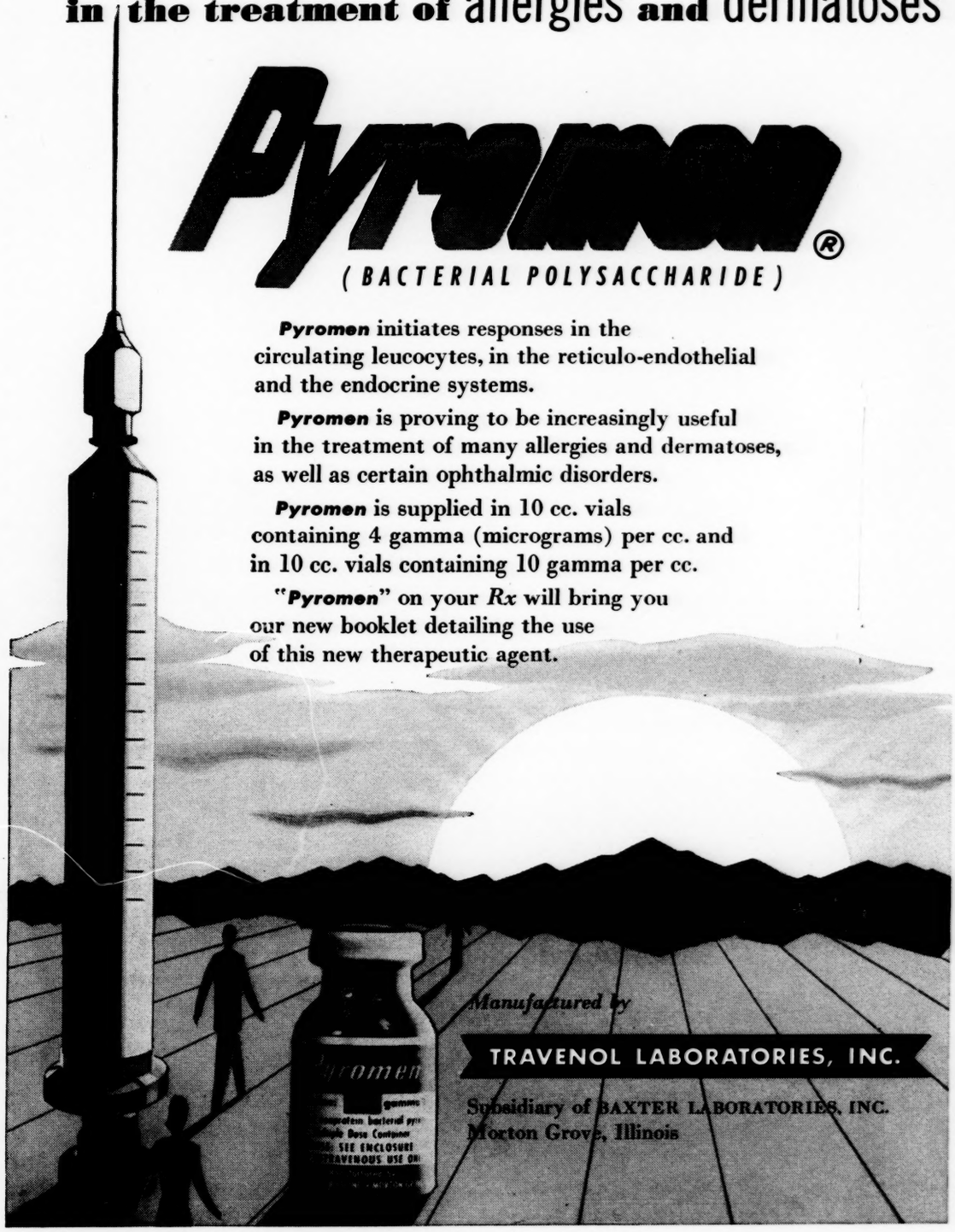

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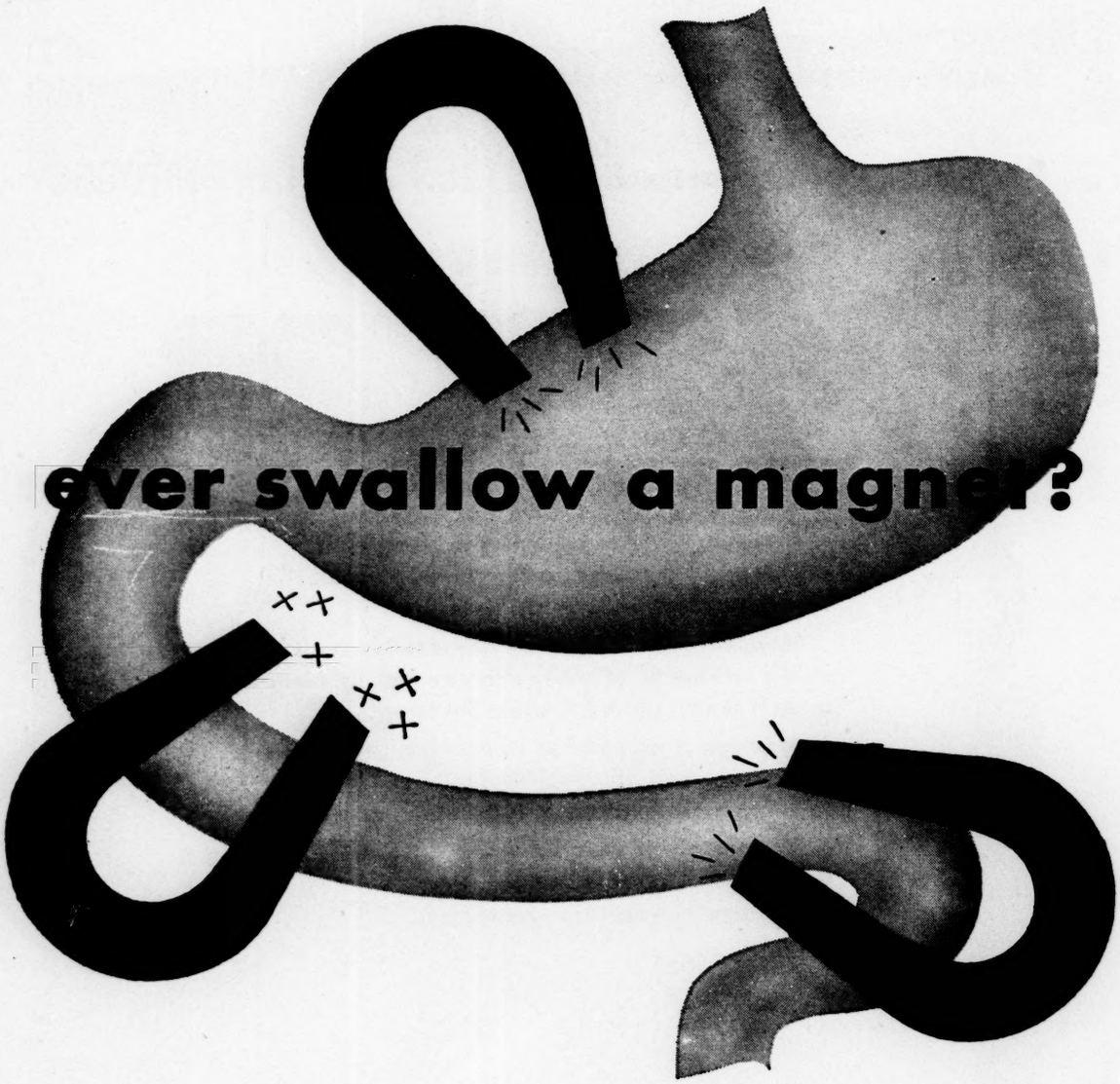

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1 Spears, M. M., and Pfeiffer, M. C. J.: Gastroenterology **8:**191 (Feb.) 1947.
2 Marks, J.: Review of Gastroenterology **16:**82 (Jan.) 1949.
3 Weiss, J.: Review of Gastroenterology **15:**826 (Nov.) 1948.
4 Wilkinson, J., and Martin, J.: Physical-Chemical Aspects of the Action of Anion Exchange Resins in Biochemical System. Arch. Biochem. **10:**205, 1946.

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References: 1. Hufford, A.R.: J.A.M.A. 122:259 (1943)
2. Talesnan, M.R.: Amer. Jrl. Obst. & Gyn. 46:146 (1943)

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Editorial

Microbes and Metchnikoff

THE theory of cellular immunity was first championed by Metchnikoff in the early eighteen eighties.[1] His thesis regarding resistance to infective disease was concisely set forth in the two following statements: (1) "There is only one constant element in immunity, whether innate or acquired, and that is phagocytosis." (2) "In general, the part played by the agglutinins in acquired immunity must be regarded as of little importance, and for that reason we abstain from basing any theory of this immunity on the agglutinative property of the body fluids." Metchnikoff's views as to the crucial role of phagocytic cells and his contention that antibodies were of little or at best of secondary importance were based upon experiments performed in the early days of bacteriology when such intracellular parasites as viruses and rickettsiae were unknown. Today, his original theory is wholly untenable as regards infectious agents that are able to propagate within the cytoplasm of phagocytic or other cells of the body. But even in the case of bacteria, such as pneumococci, that are known to be destroyed by phagocytosis, Metchnikoff's cellular theory has never been accepted. Its rejection has been due primarily to an impressive body of experimental evidence which indicates that fully encapsulated pneumococci cannot be phagocyted unless previously opsonized with specific antibody.[2]

The importance of type-specific immune bodies in pneumococcal pneumonia was clearly established by the brilliant studies of Avery, Cole, Dochez, Heidelberger, Goebel and others at the Rockefeller Hospital and of Enders and Ward at the Harvard Medical School.[3] The isolation and chemical identification of the capsular antigen and the demonstration that pathogenicity is directly related to the capsule of the pneumococcal cell are among the most significant achievements of contemporary microbiology. Not only did they lead to a clearer understanding of the host-parasite relationships in pneumococcal pneumonia (and certain other closely related bacterial diseases) but they resulted also in the development of a highly effective form of antipneumococcal therapy. In addition, they seemed to prove beyond the slightest doubt that antibodies play a major role in recovery.

There remained, however, certain clinical and experimental observations which appeared to contradict the theory that antibodies were essential for recovery. First, it is well known that the spontaneous crisis which frequently occurs in untreated pneumococcal pneumonia does not always coincide with the appearance of circulating antibody. In fact, numerous cases have been reported in which immune bodies could not be detected in the blood until many days after the subsidence of fever and the disappearance of signs of active infection.[4] Secondly, Robertson clearly showed in careful histologic studies of experimental canine pneumonia that pneumococci were phagocyted and destroyed in the pneumonic exudate during the early stages of infection when no antibody was demonstrable in the circulation.[5] Thirdly, early treatment with sulfonamides was shown to effect recovery in the absence of circulating immune bodies in spite of the fact that the sulfonamide drugs themselves have little if any bactericidal effect upon the pneumococcus.[6]

These apparently unexplained facts prompted a critical re-examination of the role of antibodies in pneumococcal pneumonia. The observations

[1] METCHNIKOFF, E. Immunity in Infective Diseases. Cambridge, 1905. University Press.

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of Robertson regarding the phagocytosis of pneumococci in the early stages of experimental pneumonia were confirmed and extended. Ingestion and apparent destruction of the infecting organisms were easily demonstrated at a time when no antibody could be detected either in the blood or at the site of infection in the lung.[7] Later studies revealed that fully encapsulated pneumococci, contrary to the accepted teachings of immunology, were readily phagocyted by leukocytes in the complete absence of antibody, provided the phagocytic cells (1) were sufficiently numerous and (2) had access to a suitable surface upon which to operate.[8] Whereas the leukocytes failed to ingest the bacteria when the cell-pneumococcus suspensions were incubated on glass slides or in test tubes, phagocytosis promptly took place when the same suspensions were incubated upon the surfaces of fresh tissues, moistened filter paper, fiber glass or cloth. Microscopic study of this phagocytic process revealed that the leukocytes phagocyted the pneumococci by trapping the individual organisms against the relatively rough surfaces over which the cells moved in their ameboid migrations. When the leukocytic suspension was sufficiently concentrated, the microorganisms were frequently phagocyted by being caught between the surfaces of two or more adjacent cells.[9] Pneumococci caught in the interstices of fibrin clots were similarly phagocyted.[10] Since in each instance the organisms were ingested only after they had been trapped against some relatively immovable surface, the process was referred to as *surface phagocytosis*. Both pneumococci and Friedländer's bacilli thus ingested in the absence of antibody were shown to be promptly killed and eventually digested.[8,11] In none of the phagocytic preparations examined microscopically was there evidence of positive chemotaxis.

Systematic histologic studies of a variety of experimental pneumococcal and Friedländer's bacillus infections in rats have provided ample indirect evidence that surface phagocytosis operates not only in the lungs but also in subcutaneous tissues,[12] in the sinuses of infected lymph nodes[12] and in the blood stream.[13] In the latter site it has been possible by means of the Sandison rabbit ear-chamber technic to observe intravascular surface phagocytosis in the living host.

The significance of surface phagocytosis lies in the fact that it takes place in the absence of antibody. It is the primary defense reaction of the host in the pre-antibody stage of infection. Admittedly less efficient than the accelerated phagocytic reaction that occurs in the presence of specific opsonins, it serves to hold the infection in check until antibodies have had time to accumulate. Occasionally it alone may effectuate recovery without the aid of immune bodies. When suitable chemotherapy is initiated, control of the infection results from the combined actions of drug and phagocytes, the latter usually operating in the absence of antibodies. In established abscesses and in suppurative lesions within the potentially "open" serous cavities and subarachnoid space, where fluid is abundant and many of the leukocytes are nonviable, phagocytosis is relatively inefficient and persistence of living organisms is the rule.

For an infectious agent to cause disease it must either be capable of surviving and multiplying in an intracellular environment or else it must remain outside of phagocytic cells long enough to multiply and cause damage to the tissues of the host. Many acute bacterial infections are due to organisms that act as extracellular parasites, their protective capsules allowing them temporarily to resist phagocytosis. The body's primary defense against such microbes is a cellular one, which depends upon the mobilization of phagocytes capable of operating in the absence of antibody. Thus in acute extracellular infections, of which pneumococcal and Friedländer's bacillus pneumonias are excellent examples, cellular immunity, in the Metchnikovian sense, plays a decisive role in natural resistance.[14]

As regards infections caused by essentially intracellular parasites, far less is known of the mechanisms of host resistance. Their elucidation would appear to depend upon future advances in a relatively unexplored field of microbiologic research—that of intracellular immunology.

W. Barry Wood, Jr., M.D.

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Clinical Studies

Treatment of H. Influenzae Meningitis with Aureomycin and Chloramphenicol*

Experience in Thirty Consecutive Cases

EMANUEL B. SCHOENBACH, M.D., HARRISON C. SPENCER, M.D. *and* JACQUES MONNIER, M.D.
Baltimore, Maryland

Of the bacterial or purulent meningitides, that caused by the gram-negative organism Hemophilus influenzae is most frequently encountered except during epidemic periods of meningococcic meningitis. Clinically, there are two varieties of influenzal meningitis which differ in their therapeutic and prognostic implications. One type is secondary to local disease or trauma in areas adjacent to the meninges such as sinusitis, mastoiditis or skull fracture. In this group a variety of H. influenzae types are encountered which cannot be serologically classified and resemble the "respiratory strains." Local surgical therapy with removal of the infectious focus together with various types of chemotherapy have often been successful in controlling the infection in the past. The majority of the infections seen among children under five years of age, however, are not associated with any overt focus and the meningitis is probably a complication of a bacteremia arising from a mild or unrecognized respiratory infection. H. influenzae type b (Pittman) is almost invariably associated with this disease. Occasionally, types a-f have been isolated from the blood and spinal fluid of such cases.

Previous to 1938 the mortality from H. influenzae meningitis among children was between 90 and 100 per cent. The extensive investigations of Fothergill, Ward and Dingle led to the development of an antibacterial horse serum which was used intravenously and, together with complement, intrathecally.[1] A somewhat lower mortality of 80 per cent was observed with this regimen. The introduction of the sulfonamide drugs resulted in a somewhat increased survival rate among adults with meningitis but did not significantly alter that observed in infants and children. The specific major contributions to therapy of type b H. influenzae meningitis were the development of a specific rabbit antiserum by Alexander[2,3] and the use of the antibiotic streptomycin.[4,5] The use of this serum either alone or in various combinations with the sulfonamides, penicillin or streptomycin resulted in reduced mortality rates in H. influenzae meningitis varying from 5 to 25 per cent.[5–8] The favorable recovery rate accentuated the resultant complications and residua.[8]

The newer antibiotics, aureomycin and chloramphenicol, have been shown to confer some protection in experimental H. influenzae infections of mice.[9,10,14] Although chloramphenicol was found to be much less active than aureomycin in animal infections, preliminary clinical trial has indicated that both antibiotics exert a beneficial effect.[9,11–14] in the naturally occurring infection in man.

The present study to assess the efficacy of aureomycin and chloramphenicol was initiated in April, 1949, at the Harriet Lane Home of the Johns Hopkins Hospital. Thirty consecutive cases of H. influenzae type b meningitis have been treated to date. Eighteen patients were treated with aureomycin and sulfadiazine during the period April, 1949, to October, 1950, while twelve patients observed from October, 1950, to March, 1951, received chloramphenicol as the only specific form of therapy. This series is of interest as the experience at the Harriet Lane Home with sulfonamides, specific rabbit serum and streptomycin from January, 1941, to November, 1948, has recently been summarized

* From the Departments of Preventive Medicine and Pediatrics, The Johns Hopkins University School of Medicine, and the Harriet Lane Home, The Johns Hopkins Hospital, Baltimore, Md.

by Crook, Clanton and Hodes.[8] The first case in the present series was included in the report by Chandler and Hodes in 1950.[9] In addition, four patients with H. influenzae type b bacteremia, who were promptly cured with these antibiotics, were observed.

The diagnosis of H. influenzae meningitis was established in all patients by examination of the spinal fluid obtained by lumbar puncture. The spinal fluid was studied with respect to its appearance, pressure, sugar content, number of cells and their differential distribution, protein content and gram stain of the centrifuged sediment. Brewer's thioglycollate medium and blood agar slants were inoculated directly with spinal fluid for bacteriologic culture. When gram-negative pleomorphic bacilli were seen a Neufeld "quellung" reaction was performed with type b specific rabbit antiserum. Lumbar punctures and spinal fluid studies, including culture, were repeated daily for the initial four days and thence on the seventh, fourteenth and twenty-first days of hospitalization. A spinal fluid examination was also performed at least four days after therapy had been discontinued and before the patient was released from the hospital. Blood cultures were obtained on admission and at intervals similar to the spinal fluid studies. Nasopharyngeal cultures were obtained initially from all patients but repeated cultures were not routinely made. The organisms isolated on culture were specifically identified. Assay of the sensitivity of type b H. influenzae to penicillin, aureomycin, chloramphenicol, terramycin, streptomycin and polymyxin D was performed employing a serial twofold dilution technic in fluid Leventhal medium.

Exploration for subdural collections of fluid was made when a history of prolonged illness was obtained, protracted febrile course was observed or localized neurologic signs were present.[15] These had not been performed prior to January, 1950 (Case 8 in Table I). Two patients required operative intervention for subdural fluid collections; in the remainder repeated aspiration sufficed. A schedule of drug therapy was adopted at the beginning of the study. Aureomycin in a daily dosage of 8 to 40 mg. per Kg. of body weight was administered intravenously. The individual dose of 3 to 10 mg. per Kg. was injected at intervals of six to twelve hours for three to four days. It was supplemented by oral aureomycin in a daily dosage of 40 to 60 mg. per Kg. divided into four to six individual doses for fourteen days. Except for local phlebitis with intravenous administration, this antibiotic schedule was well tolerated. Sulfadiazine was employed in addition to aureomycin. An initial dose of 40 to 100 mg. per Kg. was administered intravenously, followed by 50 mg. per Kg. subcutaneously every eight hours for two to five days in 0.5 per cent solution. Oral sulfadiazine was instituted as soon as possible and the patient received 150 to 300 mg. per Kg. daily for a total period of twenty-one days of sulfonamide therapy. Three patients developed temporary hematuria from this medication.

Chloramphenicol therapy was employed for a period of two to three weeks. Oral dosage alone was employed in six cases. Intravenous followed by oral drug was employed in two instances and intramuscular drug followed by oral chloramphenicol was administered to four patients. The oral dosage of chloramphenicol, when this was the sole form of therapy, was 50 mg. per Kg. initially followed by 100 mg. per Kg. daily divided into four equal parts. The intravenous preparation was a 25 per cent solution of chloramphenicol in 50 per cent dimethyl acetamide. The dosage employed was 10 mg. per Kg. four times a day. The intramuscular preparation consisted of microcrystalline chloramphenicol suspended in physiologic saline (1 gm. chloramphenicol per 4 cc.) and was administered in a dosage of 50 mg. per Kg. every twelve hours. This preparation was well tolerated locally and resulted in prompt blood levels which were maintained for at least the twelve-hour period employed. The intravenous and intramuscular preparations are at present available only for experimental investigation. Studies on the blood and spinal fluid concentration, of chloramphenicol were performed by adding serial twofold dilutions of the body fluid to broth employing K. pneumonia type A as the test organism.

One patient received streptomycin and specific rabbit antiserum in addition to the aureomycin and sulfadiazine because of prolonged fever which was probably the result of an unrecognized subdural collection of fluid.

The details of drug therapy for each patient are presented in Tables I and II. An electroencephalogram, audiometric study and evaluation of mental status were performed before discharge from the hospital and during the follow-up periods in most cases.

TABLE 1

H. INFLUENZAE MENINGITIS TREATED WITH AUREOMYCIN AND SULFADIAZINE

Name	Age, Color, Sex	Admission: Day of Disease	Admission: Temp. °F.	Admission: Severity of Symptoms	Admission: Bacteriology NP	Admission: Bacteriology Bl.	Admission: Bacteriology CSF	W.B.C. Blood	W.B.C. CSF	Treatment: mg./Kg.	Treatment: Route	Treatment: Days	Remarks
1. W. C.	51 mo. W/M	2	101.2	3+	+*	+	+	19,000	12,000	A 8	I.V.	1	Died 33 hr. after admission; CSF sterile
										A 50	Oral	1	
										S 50	I.V.	1	
										S 150	S.C.	2	
2. C. H.	6 mo. C/M	4	101.4	2+	+	−	+	21,000	2,500	A 10	I.V.	4	Afebrile 4th hosp. day; CSF sterile 2nd hosp. day; no complications
										A 50	Oral	14	
										S 40	I.V.	1	
										S 100	Oral	19	
3. S. B.	10 mo. W/F	9	102.8	3+	+	+	+	60,000	700	A 10	I.V.		Died 18 hr. after admission; CSF still positive
										A 20	Oral		
										S 30	I.V.		
										S 60	S.C.		
4. R. S.	11 mo. C/M	10	101.2	2+	−	+	+	18,000	1,250	A 10	I.V.	3	Afebrile 5th hosp. day; CSF sterile 3rd hosp. day; relapse 24 hr. after discharge
a)										A 50	Oral	13	
										S 50	S.C.	1	
										S 230	Oral	21	
b)		1	102.6	2+	−	−	+	17,000	2,500	A 14	I.V.	6	Afebrile 8th hosp. day; CSF sterile 2nd hosp. day; no complications
										A 50	Oral	21	
										S 200	Oral	28	
5. P. C.	5 mo. C/F	5	103.8	3+	0	+	+	13,600	6,400	A 40	I.V.	2	Afebrile 5th hosp. day; CSF sterile 3rd hosp. day; left spastic hemiplegia slowly cleared; subdurals not done; I.Q. evaluation Feb. 1951, normal intelligence
										A 50	Oral	21	
										S 150	S.C.	1	
										S 200	Oral	31	
6. J. A.	6 mo. C/M	6	101.8	2+	+	+	+	10,650	390	A 10	I.V.	3	Afebrile 11th hosp. day; aureo. increased I.V. due to rise in CSF cells to 5,600 on 4th hosp. day; CSF positive till 4th hosp. day; no residual complications; subdurals not done
										A 40	I.V.	3	
										A 50	Oral	21	
										S 150	S.C.	1	
										S 200	Oral	27	
7. M. B.	20 mo. W/M	5	101	3+	+	+	+	14,600	1,500	A 35	I.V.	4	Afebrile 6th hosp. day; CSF sterile 3rd hosp. day; no complications
										A 50	Oral	18	
										S 50	S.C.	1	
										S 200	Oral	24	
8. W. K.	5 mo. W/M	29	100.8	3+	0	+	+	27,200	900	A 40	I.V.	4	Febrile till 17th hosp. day when right trephine was done, then afebrile; bilateral subdurals—one cleared—right trephined; CSF sterile 3rd hosp. day; severe retardation with double hemiparesis
										A 50	Oral	34	
										S 170	Oral	43	
9. Y. B.	7 mo. C/F	2	103.4	2+	−	+	+	35,850	940	A 40	I.V.	4	Afebrile 2nd hosp. day; CSF sterile 3rd hosp. day; no complications
										A 50	Oral	14	
										S 225	S.C.	3	
										S 150	Oral	20	
10. B. W.	6 mo. C/F	9	101.8	3+	−	+	+	40,000	382	A 40	I.V.	5	Febrile till 24th hosp. day; CSF sterile 13th hosp. day; residual neurologic damage; hearing loss; (aureomycin given with amphogel)
										A 50	Oral	32	
										S 195	S.C.	30	
										S 200	Oral	8	
										S 250	Oral	5	
										ST (50	I.M.	17	
										ST (25	mg. I.T.	5)	
										SER (150	mg. I.V.	1)	
11. F. L.	32 mo. C/F	5	103.2	2+	0	−	+	13,000	406	A 20	I.V.	4	Afebrile 2nd hosp. day; CSF sterile 5th hosp. day; vomited medication; no complications
										A 50	Oral	14	
										S 150	Oral	21	
12. R. D.	11 mo. W/M	18	101.8	2+	−	+	+	19,000	1,440	A 40	I.V.	4	Afebrile 3rd hosp. day; CSF sterile 2nd hosp. day; no complications
										A 50	Oral	14	
										S 225	S.C.	4	
										S 200	Oral	17	
13. S. G.	19 mo. C/F	16	101	2+	−	−	+	20,000	3,200	A 40	I.V.	3	Afebrile 2nd hosp. day; CSF sterile 3rd hosp. day; no complications
										A 50	Oral	14	
										S 200	S.C.	4	
										S 250	Oral	16	
14. S. G.	9 mo. W/F	17	100.4	3+	−	−	+	14,200	25,800	A 40	I.V.	4	Afebrile 6th hosp. day; CSF sterile 2nd hosp. day; vomited medications; mental retardation
										A 50	Oral	18	
										S 200	S.C.	5	
										S 200	Oral	14	
15. L. S.	7 mo. C/M	2	104.4	3+	+	+	+	11,200	1,300	A 40	I.V.	3	Afebrile 8th hosp. day; CSF sterile 4th hosp. day; bilateral subdurals; pressure sore left foot; plastic repair; sudden death
										A 50	Oral	16	
										S 300	S.C.	4	
										S 250	Oral	30	
16. L. E.	3 mo.	6	100.2	2+	−	−	+	12,300	250	A 40	I.V.	3	Afebrile 2nd hosp. day; CSF sterile 2nd hosp. day; no complications
										A 50	Oral	14	
										S 50	S.C.	1	
										S 150	Oral	21	
17. M. W.	3 mo. C/M	7	105.4	2+	0	+	+	26,500	4,500	A 40	I.V.	4	Afebrile 2nd hosp. day; CSF sterile 2nd hosp. day; small bilateral subdural effusions, cleared in one week
										A 50	Oral	14	
										S 50	I.V.	1	
										S 200	Oral	21	
18. B. T.	8 mo. C/M	3	101.2	2+	−	+	+	25,000	1,300	A 40	I.V.	3	Afebrile 5th hosp. day; CSF sterile 3rd hosp. day; bilateral subdurals relieved by tapping; neurologic residual, spastic paraplegia
										A 50	Oral	14	
										S 50	I.V.	1	
										S 300	S.C.	2	
										S 300	Oral	42	

3+—severe
2+—moderate
A—aureomycin
S—sulfadiazine
NP—nasopharynx
ST—streptomycin
+*—indicates H. influenzae type B
SER—specific anti-influenzal rabbit serum type B. dosage expressed as milligrams of antibody nitrogen.

CLINICAL OBSERVATIONS

The observations on these thirty patients with influenzal meningitis are summarized in Tables I and II and are graphically presented in Figure 1. It may be noted that of the twelve patients who received chloramphenicol only five or 41 per cent, were under one year of age, while fourteen or 78 per cent of the group treated with the combination of aureomycin and sulfadiazine were within this age group. In addition to age, another index of severity which may be employed is the presence of coma or convulsions before institution of therapy. Seven of the patients treated with chloramphenicol (58 per cent) and eight (44 per cent) of those receiving aureomycin were thus classified. Although determination of the exact time of onset is notoriously difficult, the two groups were essentially comparable with respect to the duration of disease before hospitalization, as estimated from the history obtained.

All spinal fluid cultures were positive for H. influenzae type b before treatment was instituted. Thirteen (72 per cent) of the aureomycin group and eleven (92 per cent) of the group receiving chloramphenicol had positive blood cultures, while the nasopharyngeal cultures were positive in 50 and 63 per cent of the two groups, respectively.

In this group of thirty patients with H. influenzae meningitis three deaths (10 per cent) were observed. Two of the patients succumbed during the period of infection. The third patient, who had been treated and cured with aureomycin and sulfadiazine, died several weeks later following an operation for plastic repair of a large skin defect. No evidence of intracranial disease was noted at postmortem examination. This latter case will be presented in detail. The fatality rate among the group receiving aureomycin and sulfadiazine thus was 17 per cent. No deaths occurred in the chloramphenicol-treated group.

Following the initiation of aureomycin and sulfonamide therapy, the spinal fluid cultures became and remained sterile within forty-eight hours in seven patients (39 per cent); seventy-two hours in fourteen (78 per cent) and within ninety-six hours in sixteen (89 per cent). In two patients a sterile spinal fluid culture was not maintained until the fifth and thirteenth hospital days. Among the patients treated with chloramphenicol the cerebrospinal fluid became and remained sterile within forty-eight hours in eight

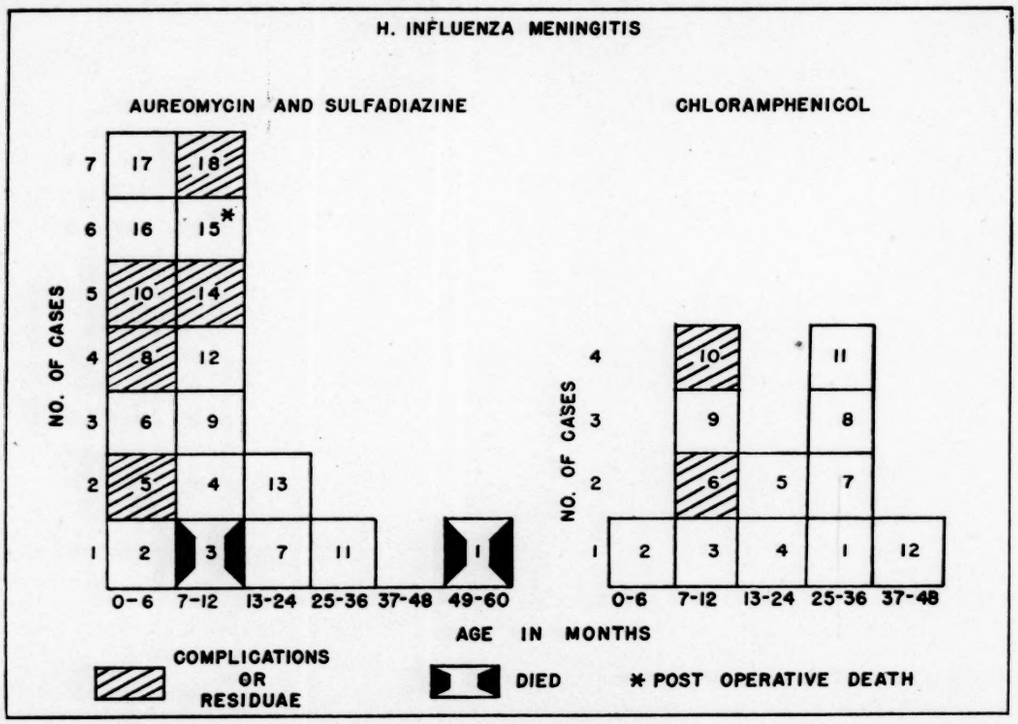

FIG. 1. Age distribution and summary of clinical observations in thirty cases of H. influenzae meningitis treated with aureomycin and sulfadiazine or chloramphenicol.

(66 per cent) and within seventy-two hours in all twelve (100 per cent).

The incidence of complications was comparatively low in this series. The chief complication encountered was the development of subdural collections of fluid. These were treated by repeated aspiration except for two patients (Table I, Case 8, and Table II, Case 10) who required trephine and surgical removal of the fluid and membrane. Deafness developed in one patient, mental retardation was observed in two patients and some paralysis was noted in seven patients. The paralysis cleared in two when examined at various intervals after discharge from the hospital; two additional patients showed marked improvement in the extent and degree of paralysis although residua were still present.

The experience in this series of patients may be illustrated with selected case reports.

1. *H. influenzae type b meningitis with prompt response to aureomycin and sulfadiazine:*

CASE 7 (A-74380). Table I. M. B., a twenty month old white male, had developed an upper respiratory infection four days before admission. Despite treatment with penicillin the child became febrile, drowsy and suffered recurrent emesis. He was therefore referred to the hospital.

TABLE II

H. INFLUENZAE MENINGITIS TREATED WITH CHLORAMPHENICOL

Name	Age, Color, Sex	Admission						W.B.C.		Treatment			Remarks
		Day of Disease	Temp. °F.	Severity of Symptoms	Bacteriology NP	Bl.	CSF	Blood	CSF	mg./Kg.	Route	Days	
1. S. B.	36 mo. W/M	5	104	3+	0	+	+	3,160	1,050	C 40 C 100	I.V. Oral	2 12	Afebrile 5th hosp. day; CSF sterile 2nd hosp. day; no complications
2. V. H.	3 mo. C/F	14	103.4	3+	−	+	+	26,800	2,600	C 40 C 100	I.V. Oral	2 26	Bilateral subdurals responded to tapping; afebrile 6th hosp. day; CSF sterile 2nd hosp. day
3. L. C.	9 mo. W/F	2	104	3+	+	+	+	4,800	21,800	C 100	Oral	22	Afebrile 5th hosp. day; negative subdurals; CSF sterile 3rd hosp. day
4. W. M.	14 mo. W/F	6	104.4	3+	+	+	+	19,000	26,500	C 100 C 25	Oral Oral	13 6	Afebrile 5th hosp. day; negative subdurals; CSF sterile 3rd hosp. day; no complications
5. L. T.	14 mo. C/F	11	100.6	2+	+	+	+	41,000	720	C 100 C 50	Oral Oral	15 6	Afebrile 3rd hosp. day; small bilateral subdural effusions, cleared with tapping; CSF sterile 3rd hosp. day
6. M. J.	9 mo. C/M	2	103.8	3+	−	+	+	18,000	5,600	C 100 C 50	Oral Oral	17 2	Afebrile 9th hosp. day; left hemiplegia cleared slowly; right subdural, responded to tapping; CSF sterile 3rd hosp. day
7. P. C.	27 mo. C/F	2	104.4	2+	+	−	+	15,000	6,600	C 100	Oral	21	Afebrile 3rd hosp day; CSF sterile 2nd hosp. day; no complications
8. M. W.	31 mo. W/M	2	104	3+	+	+	+	15,000	5,000	C 100 100	I.M. Oral	6 13	Afebrile 6th hosp. day; CSF sterile 2nd hosp. day; no complications
9. J. P.	7 mo. W/F	3	103.8	2+	+	+	+	12,350	3,800	C 100 C 100	I.M. Oral	10 10	Afebrile 7th hosp. day; subdurals negative; CSF sterile 2nd hosp. day; no complications
10. J. B.	7 mo. C/F	3	102.4	3+	−	+	+	13,600	7,200	C 100 A 50 ST 50	Oral Oral I.M.	36 2 17	Afebrile 18th day; subdural hematoma with hemiplegia; CSF sterile 2nd hosp. day
11. M. B.	32 mo. W/F	5	101.4	2+	−	+	+	22,600	25,000	C 100 C 100	I.M. Oral	4 11	Afebrile 6th hosp. day; CSF sterile 2nd hosp. day; no complications
12. B. P.	39 mo. C/M	5	103.4	2+	+	+	+	19,560	8,050	C 100	I.M.	21	Afebrile 3rd hosp. day; CSF sterile 2nd hosp. day; no complications

3+—severe
2+—moderate
A—aureomycin
ST—streptomycin
C —chloramphenicol
NP—nasopharynx

On physical examination he appeared acutely ill, drowsy and irritable. The tonsils were enlarged and the pharynx was injected. The neck was held rigid and positive Kernig and Brudzinski signs were present. The clinical course is graphically presented in Figure 2.

Significant laboratory studies showed the white blood cell count to be 14,600 per cu. mm., of which 57 per cent were polymorphonuclears. The spinal fluid was cloudy, showed a positive Pandy reaction and marked reduction in sugar content. There were 500 leukocytes per cu. mm., 90 per cent of which were polymorphonuclear. The smear of this fluid showed gram-negative pleomorphic bacilli which were typed directly with anti-influenzal serum. Culture of the naso-

pharynx, blood and spinal fluid were subsequently reported as positive for H. influenzae type b.

Sodium sulfadiazine was administered subcutaneously immediately upon admission and every eight hours for the first day. Two grams

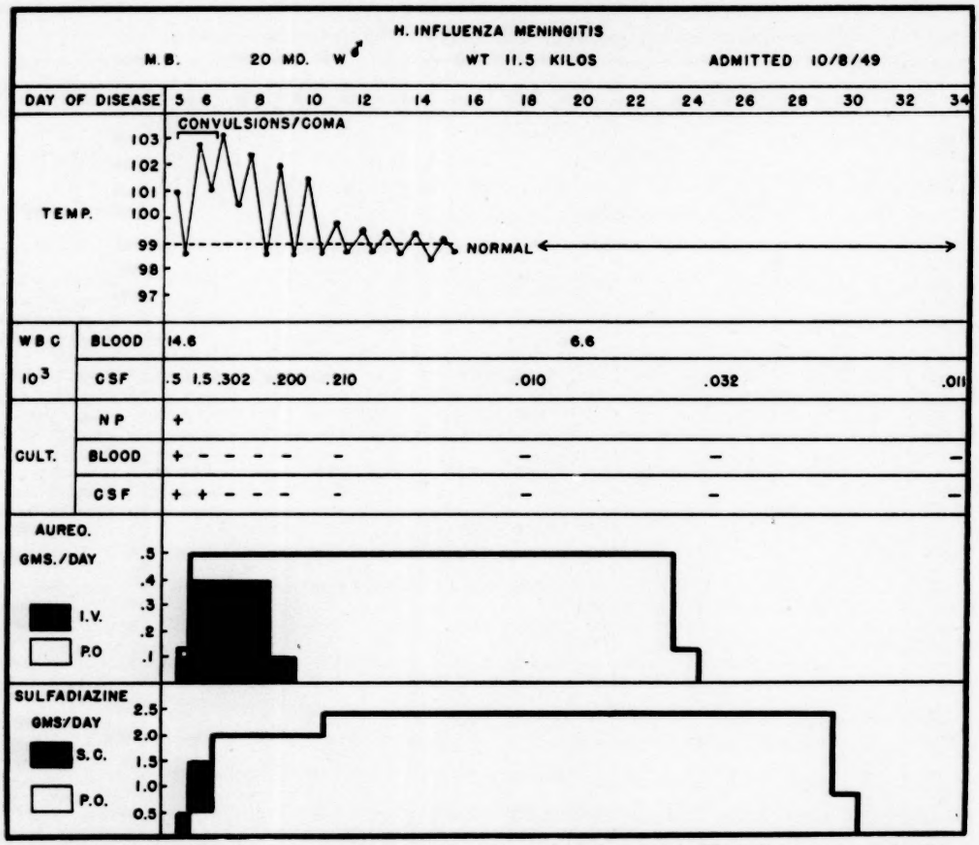
H. INFLUENZA MENINGITIS
M. B. 20 MO. W ♂ WT 11.5 KILOS ADMITTED 10/8/49
DAY OF DISEASE 5 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34
CONVULSIONS/COMA
TEMP. 103 102 101 100 99 98 97
NORMAL
WBC 10³ BLOOD 14.6 6.6
CSF .5 1.5 .302 .200 .210 .010 .032 .011
CULT. NP +
BLOOD + - - - - - - - - -
CSF + + - - - - - - -
AUREO. GMS./DAY .5 .4 .3 .2 .1
I.V.
P.O.
SULFADIAZINE GMS/DAY 2.5 2.0 1.5 1.0 0.5
S.C.
P.O.

FIG. 2. Chart of M. B., a twenty month old male infant with H. influenzae meningitis, treated with aureomycin and sulfadiazine.

were then administered orally daily for the ensuing twenty-four-day period. In addition, he received 100 mg. of aureomycin intravenously every six hours for the first three days and every twelve hours for the next day. Oral aureomycin, 500 mg. per day, was also administered for the first eighteen days of hospitalization. With this combined therapy the spinal fluid became sterile within seventy-two hours and the patient became afebrile and asymptomatic after the fifth hospital day. There was no evidence of drug toxicity or complications of the infection and the patient was released on the twenty-ninth hospital day. Follow-up examination six months after discharge showed the child to be perfectly normal without any residua or evidence of mental retardation.

2. *Patient with subdural effusion complicating H. influenzae meningitis treated with aureomycin and sulfadiazine:*

CASE 8 (A-74049). Table I. W. K. was a five month old white male who had been ill for twenty-eight days with an acute respiratory infection associated with fever and convulsions. Because of continued illness and lack of response to various therapeutic regimens the child was brought to the Harriet Lane Home of the Johns Hopkins Hospital. Physical examination disclosed a comatose, acutely ill infant with a temperature of 100.8°F. He weighed 6.0 Kg. Bulging of the anterior fontanelle was evident. The sutures were widely separated and parietal bossing of the head was present. No pupillary light reflex was elicited although ophthalmoscopic examination of the fundi did not show any abnormalities. The neck was held rigid and the deep tendon reflexes were hyperactive. Laboratory examination showed that the hemoglobin was 10.5 gm. per 100 ml. The white blood cell count was 27,200 per cu. mm., 72 per cent

of which were polymorphonuclears. The fluid obtained by lumbar puncture was cloudy with 4+ Pandy reaction, contained only a trace of sugar and 900 cells per cu. mm., of which 40 per cent were polymorphonuclear. Numerous pleomorphic gram-negative bacilli were seen on smear and were typed directly with H. influenzae type b antiserum. Subdural aspiration disclosed xanthochromic fluid bilaterally which contained 8,000 cells and many gram-negative bacilli. Culture of the blood, spinal fluid and subdural fluids was consistently positive for H. influenzae type b.

The patient was treated with aureomycin. He received 60 mg. intravenously every six hours for four days. In addition, he received 300 mg. of aureomycin orally daily for thirty-four days. Oral sulfadiazine was given in an initial dose of 500 mg. and then 250 mg. every six hours for forty-three days. The patient remained febrile during the first two and one-half weeks of hospitalization although the blood and spinal fluid cultures became negative after seventy-two hours. Daily subdural aspirations were performed. After the third day no fluid was obtained from the left side; but because nineteen consecutive taps on the right side still netted 10 to 35 cc. of xanthochromic fluid, large burr holes were made in the right temporal and parietal regions and a subdural collection of fluid was evacuated from the region of the motor cortex. The infant withstood the operative procedure without any untoward manifestations and became afebrile postoperatively. The subsequent hospital course was uneventful, and he was discharged 55 days after his admission. Follow-up examination seven months later showed that the child was somewhat mentally retarded and a slight degree of paralysis of the arms and legs, more marked on the right side, was present. He had had no convulsions and there was no evidence of hearing loss.

3. *Relapse of H. influenzae meningitis after treatment with aureomycin and sulfadiazine:*

Case 4 (A-71506). Table 1. R. S. was an eleven month old colored male who weighed 6.5 Kg. He had had a persistent nasal discharge, fever, drowsiness and irritability for ten days preceding admission. Bulging of the anterior fontanelle became evident and he was referred to the hospital. Upon admission the child appeared to be poorly nourished, lethargic and irritable. The anterior fontanelle was bulging and tense. The neck resisted flexion and the tendon reflexes were hyperactive. The temperature was 101.2°F. and he appeared acutely ill. Laboratory studies showed that the hemoglobin was 8 gm. per 100 ml. and the white blood cell count was 18,000 per cu. mm. The Pandy test on the spinal fluid was 2+; the sugar content was reduced, and 1,250 cells per cu. mm. were present, 80 per cent of which were polymorphonuclear. Smears from the spinal fluid showed many gram-negative pleomorphic bacilli which were typed directly with specific anti-influenzal serum. Blood and spinal fluid cultures were subsequently reported as positive for H. influenzae type b.

The child was treated with 325 mg. of sulfadiazine subcutaneously followed by a daily dose of 1.5 gm. orally for twenty-one days. In addition, he received 40 mg. of aureomycin intravenously every twelve hours for three days and 300 mg. per day orally for fourteen days. The spinal fluid became sterile on the third hospital day and the patient became afebrile on the fifth hospital day. Repeated lumbar punctures thereafter yielded normal fluid. He was discharged from the hospital asymptomatic and afebrile three weeks after admission.

Two days later the patient returned to the hospital because of fever, listlessness and anorexia. His temperature was 102.6°F. Spinal fluid examination showed it to be cloudy with positive Pandy test, moderately reduced sugar content and a pleocytosis of 2,500 cells. Gram-negative bacilli were again seen on smear and were identified as H. influenzae type b by direct "quellung." The spinal fluid culture was subsequently reported as positive although a blood culture drawn at that time was sterile.

He was treated with an initial dose of 750 mg. of sulfadiazine orally, followed by 1 gm. daily for twenty-eight days. In addition he received 45 mg. of aureomycin intravenously twice daily for six days and 360 mg. per day orally for twenty-one days. The spinal fluid was sterile on the second hospital day and the patient became afebrile and asymptomatic at the end of the first hospital week. After treatment was discontinued the patient was closely observed, without any evidence of relapse. He was discharged completely normal. The medication was well tolerated and there were no signs of toxicity. Follow-up examination nineteen months later showed no evidence of impairment of hearing, mental retardation or other complications.

4. *Deaths observed among patients with H. influenzae meningitis treated with aureomycin and sulfadiazine:*

Case 1 (A69600) Table 1. W. C. was a fifty-one month old white male who was admitted because of fever, recurrent vomiting and stupor of thirteen hours' duration. A physician had given him parenteral penicillin but because his symptoms persisted and he appeared to become sicker he was referred to the hospital.

Physical examination disclosed a severely ill boy with a temperature of 101.2°F., pulse 140 and respiration 36. His weight was 19 Kg. Hydration appeared good. He was responsive only to painful stimuli. The neck was held rigid and Kernig and Brudzinski signs were present. The tonsils were enlarged and acutely inflamed. Laboratory examination revealed a white count of 19,000 per cu. mm., 96 per cent of which were polymorphonuclears. The spinal fluid was cloudy and under increased pressure (400 mm. of water). The Pandy test on the spinal fluid was 4+. There were 12,000 cells per cu. mm., 90 per cent of which were polymorphonuclear and a gram stain showed numerous pleomorphic rods which were identified as type b H. influenzae by the "Quellung" reaction. Culture of the nasopharynx, throat, blood and spinal fluid were subsequently reported as positive for H. influenzae type b.

The child received 950 mg. of sulfadiazine intravenously and 950 mg. of sulfadiazine subcutaneously immediately. The subcutaneous sulfadiazine was repeated every eight hours. In addition, 75 mg. of aureomycin intravenously every twelve hours, and 250 mg. orally every six hours were administered. The patient remained comatose and twelve hours after his admission he began to have convulsions. A repeated lumbar puncture on the second hospital day revealed the spinal fluid to be cloudy, under a pressure of 210 mm. of water, and contained 24,000 cells, 95 per cent of which were polymorphonuclear. No organisms were seen on smear but cultures were positive forty-eight hours later for H. influenzae type b. The child's temperature ranged between 100.4° and 103.2°F. and his general condition remained essentially unchanged, with repeated convulsive episodes. He died on the morning of the third hospital day, thirty-three hours after admission. Postmortem blood and spinal fluid cultures were sterile. Acute purulent meningitis, cerebellar edema and tubular degeneration in the adrenals were noted at autopsy.

Case 3 (A70010) Table 1. S. B. was a ten month old white female who became febrile and drowsy eight days before admission to the hospital. She received penicillin following a tentative diagnosis of pneumonia. During the next seven days she continued to be febrile and became semi-comatose. She held her body rigid. Forty-eight hours before admission repeated generalized clonic convulsions appeared.

The child was acutely ill, semi-comatose with shallow, irregular respirations. Her temperature was 102.8°F. The infant maintained an opisthotonic attitude. The anterior fontanelle was sunken. The neck was held rigid and Brudzinski and Kernig signs were present. The liver edge was palpable two fingerbreadths below the costal margin. Laboratory studies showed the child to have a hemoglobin of 10 gm. per 100 ml. and a white blood count of 60,000 per cu. mm., 70 per cent of which were polymorphonuclear. The spinal fluid was cloudy with positive Pandy reaction, negative qualitative test for sugar, and contained 700 leukocytes per cu. mm. There were numerous gram-negative pleomorphic bacilli which were typed with specific anti-influenzal serum. Nasopharyngeal, throat, blood and spinal fluid cultures were subsequently reported as positive for H. influenzae type b.

Sulfadiazine was administered upon admission, 250 mg. intravenously and 250 mg. subcutaneously. The subcutaneous administration was continued at eight-hour intervals. Aureomycin was prescribed initially in a dosage of 40 mg. intravenously every twelve hours and 50 mg. orally every four hours. However, because of marked emesis the oral drug was discontinued and 250 mg. of aureomycin was given every four hours per rectum. Supportive therapy with plasma, blood, digitalis and oxygen was also employed but despite these measures the infant continued to have repeated convulsions. On the second hospital day a cisternal tap was performed and cloudy fluid containing 25,000 leukocytes was observed. The fluid contained many organisms on smear and culture was subsequently positive for H. influenzae type b. Blood culture obtained at this time was sterile. The infant died eighteen hours after admission. Permission for postmortem examination was not obtained.

Case 15 (A79365) Table 1. L. S., a six month old colored male, was admitted to the hospital

because of fever for approximately 10 hours, marked irritability and a convulsion. Two weeks before the child had had a mild respiratory infection unassociated with fever. Upon admission to the hospital his temperature was 105°F. and he appeared acutely ill. His weight was 9.0 kg.

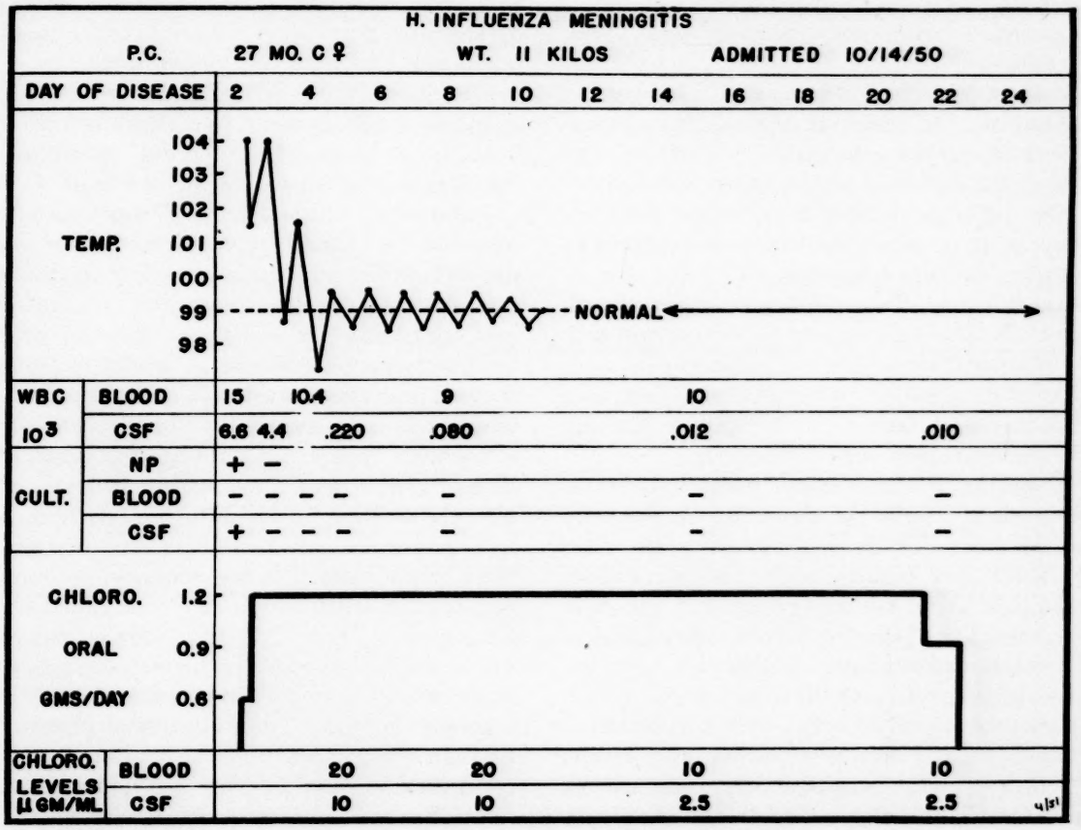

FIG. 3. Chart of P. C., a twenty-seven month old female infant with H. influenzae meningitis, treated with oral chloramphenicol.

Physical examination showed a drowsy, irritable, convulsing infant. His neck was supple. Spinal fluid was cloudy with a 2+ reaction to the Pandy reagent. Sugar was moderately reduced. There were 1,400 cells per cu. mm. in the fluid and the smear showed numerous gram-negative pleomorphic bacilli which were typed with specific anti-influenzal serum. Blood and spinal fluid cultures were subsequently positive for H. influenzae type b.

The infant was treated with sulfadiazine 900 mg. subcutaneously immediately and every eight hours for four days. Four hundred mg. were then administered orally every four hours for the ensuing thirty days. Aureomycin was also administered, 90 mg. intravenously every six hours for the first three days supplemented by 75 mg. orally every four hours. The oral dose was continued for a total period of sixteen days. On this combined therapy, blood and spinal fluid cultures became and remained sterile on the second hospital day. The infant became afebrile at the end of the first hospital week at which time the spinal fluid was normal. A subdural tap on the eighth hospital day showed xanthochromic fluid. Subdural aspirations were repeated daily and as much as 70 ml. of xanthochromic fluid were withdrawn from the left side on one occasion. The bilateral subdural collections of fluid appeared to clear after eleven days of aspiration. The child remained well except that on the twenty-third hospital day he had a right-sided Jacksonian convulsion without loss of consciousness. Following this, physical examination did not disclose any evident focus and the child appeared well.

An area of pressure necrosis about one heel had developed and it was decided to perform a plastic repair of this area. On the thirty-seventh hospital day a split thickness graft was applied under general ether anesthesia. The operation lasted one hour and fifteen minutes. Postopera-

tively the child appeared to respond well but one hour later he was discovered dead in bed. Postmortem examination did not disclose any cause of death. No subdural collection of fluid was present. There was no evidence of cortical destruction. Spinal fluid and blood cultures were negative.

5. *Treatment with oral chloramphenicol with prompt response:*

Case 7 (A-64780). Table II. P. C., a twenty-seven month old colored female, developed an upper respiratory infection manifested by rhinitis and cough two weeks before admission. One day prior to hospitalization she became drowsy, so that when seen in the outpatient department she was stuporous.

The significant clinical features are outlined in Figure 3. She was acutely ill, stuporous and had a temperature of 104.4°F. Pharyngeal and tonsillar inflammation were present. She was opisthotonic and had nuchal rigidity; Kernig and Brudzinski signs were elicited.

The pertinent laboratory studies were a leukocytosis of 15,000 per cu. mm., 68 per cent of which were polymorphonuclear cells. The spinal fluid was cloudy with positive Pandy reaction, and sugar content reduced; 6,600 cells per cu. mm. were present, 92 per cent of which were polymorphonuclear leukocytes. Gram-negative pleomorphic bacilli were seen on smear and they were typed directly, with specific anti-influenzal serum. Nasopharyngeal and spinal fluid cultures were subsequently reported as positive for H. influenzae type b. Blood culture was sterile.

She received an initial dose of 0.6 gm. of chloramphenicol orally and then 0.3 gm. every six hours for twenty days. Blood and spinal fluid antibiotic levels are noted in Figure 3. The organism was completely inhibited *in vitro* by 0.156 micrograms per ml. of penicillin, 2.5 micrograms per ml. of aureomycin, 0.625 micrograms per ml. of chloramphenicol, 5.0 micrograms per ml. of terramycin, 3.1 micrograms per ml. of streptomycin and 1.25 micrograms per ml. of polymyxin D.

The spinal fluid became sterile on the second day and the patient became afebrile on the third hospital day. Convalescence was uneventful and no complications or evidence of drug toxicity were observed. She was discharged on the twenty-fourth hospital day and remained well.

6. *Treatment with intramuscular chloramphenicol with prompt response:*

Case 8 (A82436) Table II. M. W., a thirty-one month old white male, had contracted a mild upper respiratory infection with nasal discharge unaccompanied by fever one week before admission. One day prior to admission it was noted that he was febrile, drowsy, irritable and had projectile vomiting. The symptoms were progressive so that upon admission he was in a coma and had recurrent convulsions.

His temperature when first observed in the outpatient clinic was 104°F. There were rales at both lung bases. The clinical course in the hospital is graphically shown in Figure 4.

Laboratory studies showed the white blood count to be 15,000 per cu. mm., 70 per cent of the cells being polymorphonuclear. Spinal fluid was cloudy with 4+ Pandy test, absent sugar, and contained 5,600 cells of which 91 per cent were polymorphonuclear. A smear of this fluid showed many gram-negative pleomorphic bacilli which could be typed by "quellung" with H. influenzae type b antiserum. Nasopharyngeal, blood and spinal fluid cultures were subsequently positive for H. influenzae type b.

The patient was immediately treated with chloramphenicol, intramuscularly, 50 mg. per Kg. of body weight (660 mg.) every twelve hours for six days. Then 325 mg. were administered orally every six hours for thirteen days. Cultures of the nasopharynx, blood and spinal fluid were negative the day after admission. During the first six hours after hospitalization the patient continued to have intermittent convulsions. His fever became progressively lower so that he became and remained afebrile after the fifth day. The spinal fluid cleared progressively and was normal during the third hospital week. The chloramphenicol was well tolerated locally and no toxic manifestations were observed.

On the fifth hospital day an electroencephalographic tracing showed an abnormal focus over the left occipital area. Two electroencephlograms obtained during the ensuing two weeks of hospitalization were normal. A follow-up examination four months after discharge from the hospital showed the boy to be well, with no evidence of hearing loss, neurologic damage or mental retardation.

7. *Treatment with chloramphenicol in a patient with H. influenzae meningitis complicated by subdural effusions:*

Case 10 (A81206). Table II. J. B. was a five month old colored female who had developed a respiratory infection associated with nasal

discharge, fever, emesis and convulsions two and one-half days before admission. She was treated with penicillin but because of the continued fever and convulsions she was referred to the Harriet Lane Home. At the time of admission her temperature was 102.4°F. and she appeared typed with anti-influenzal serum. The blood and spinal fluid were subsequently positive for H. influenzae type b. The patient received 300 mg. of chloramphenicol orally upon admission and this was followed by 150 mg. every six hours for thirty-six days. The blood and spinal

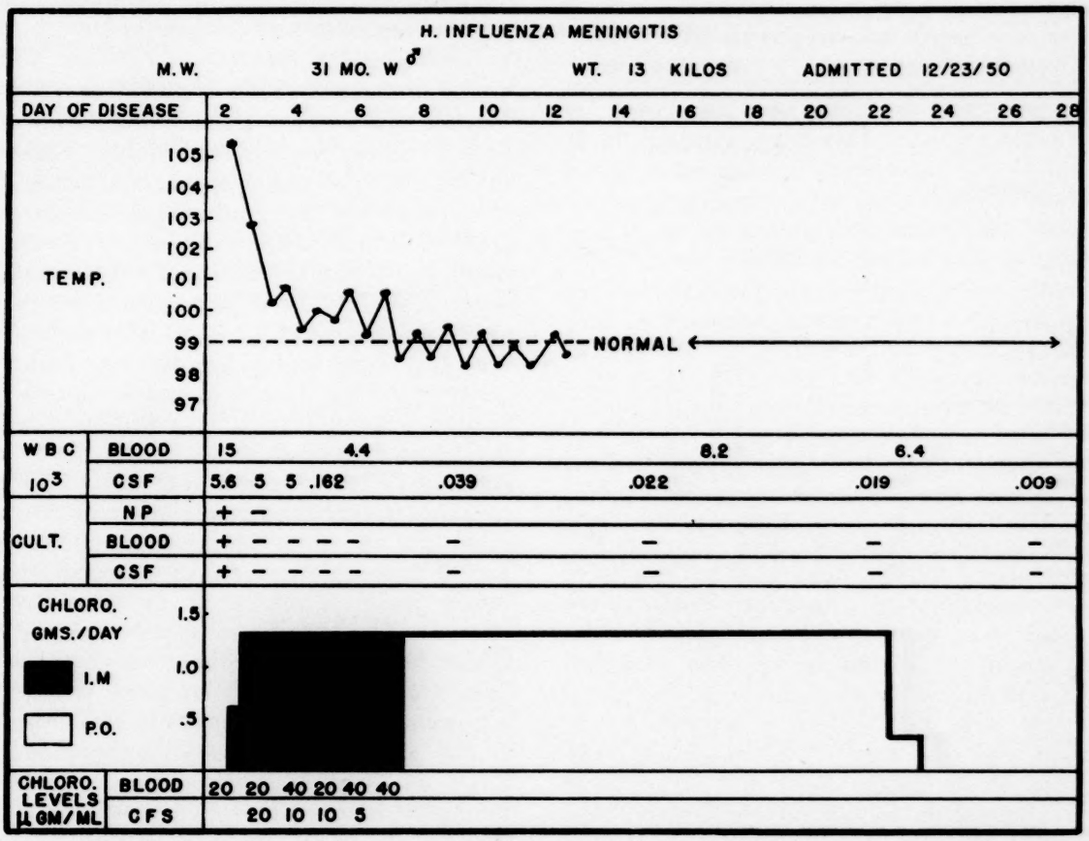

FIG. 4. Chart of M. W., a thirty-one month old male infant with H. influenzae meningitis, treated with intra-muscular microcrystalline chloramphenicol.

acutely ill, restless, with difficulty in respiration. Her weight was 5.8 Kg. She maintained herself in an opisthotonic position. The extremities were spastic and tendon reflexes hyperactive. The anterior fontanelle was tense and bulging. Her throat was inflamed and she resisted flexion of the neck.

Laboratory studies showed the hemoglobin to be 8.0 gm. per 100 ml. and the white blood count was 13,000 per cu. mm., which when repeated that day was 23,000 with approximately 60 per cent of the cells polymorphonuclear. The spinal fluid was cloudy, showed a 4+ Pandy reaction, reduced sugar content, and contained 7,200 cells of which 90 per cent were polymorphonuclear. Gram-negative bacilli were present in the spinal fluid and could be specifically

fluid cultures were sterile within twenty-four hours and remained so throughout the entire period of hospitalization. The patient, however, continued to have fever, nuchal rigidity and bulging anterior fontanelle. On the eleventh hospital day she received aureomycin 75 mg. orally every six hours for two days, and 150 mg. of streptomycin intramuscularly for seventeen days, in addition to the chloramphenicol. Despite the continued therapy the patient remained febrile and pleocytosis of the spinal fluid persisted. On the third and fourth hospital days subdural taps were performed and several ml. of thick purulent xanthochromic fluid containing 96,000 white cells per cu. mm. were aspirated from the subdural spaces. The taps were repeated on five subsequent occasions without

recovering any fluid. The patient was discharged on the forty-first hospital day with a normal spinal fluid except for the presence of 23 mononuclear cells.

She was readmitted five days later because of vomiting and left hemiplegia. She was afebrile and in no distress. Kernig sign was positive; movements of the left arm and left leg were limited and hypertonic. Sustained clonus of the left ankle was present. The peripheral white blood count was 16,350 per cu. mm. of which 52 per cent were polymorphonuclear. The spinal fluid was clear but showed a positive Pandy reaction and contained 21 mononuclear cells. Cultures of the spinal fluid and blood were sterile. Aspiration of the subdural spaces was performed, 50 cc. of bloody xanthochromic fluid was aspirated from the right side at the extreme temporal angle of the anterior fontanelle. Aspirations were repeated daily for five days and every other day thereafter until the sixteenth hospital day when no further fluid was obtained. An electroencephalogram showed a focus of low voltage over the right parieto-occipital area and abnormal discharge over the right frontal area. On the nineteenth hospital day, therefore, the right frontal region was trephined and a rather thick, greenish membrane containing no fluid or clot was observed. The membrane was stripped from the arachnoid and as much removed as possible. The underlying brain tissue appeared yellow and necrotic. Postoperatively the patient remained afebrile but the hemiplegia persisted. The repeat electroencephalogram one week after operation was interpreted as normal and the patient was discharged three days later. Follow-up examination after two months showed that the infant was in good health. There was no evidence of hearing loss; movement of the left leg and arm was active but she did not grasp well with the left hand and the tendon reflexes on the left side were still somewhat more active than the right. The ankle clonus had disappeared.

TABLE III
SUMMARY OF ANTIBIOTIC SENSITIVITY NOTED WITH TWENTY-TWO CASE STRAINS OF H. INFLUENZAE TYPE b

Antibiotic	Minimal Inhibitory Concentration (mcg./ml.)	
	Range	Median
Penicillin G (1.66 units/mcg.)	.156 –10.0	0.78
Aureomycin	.156 – 2.5	0.39
Chloramphenicol	.156 – 5.0	0.625
Terramycin	.156 – 5.0	0.39
Streptomycin	1.56 – 3.1	1.56
Polymyxin D	.0078– 1.25	0.15

IN VITRO STUDIES

Assay of the blood and spinal fluid for aureomycin content was attempted but, because of the instability of this antibiotic and the presence of sulfonamide, the results could not be evaluated with any degree of accuracy. Patients treated with oral chloramphenicol alone showed serum levels of 5 to 40 micrograms per ml. and spinal fluid levels of 2.5 to 10 micrograms when the antibiotic was administered daily. The microcrystalline chloramphenicol is a new preparation. Four normal infants without disease of the central nervous system had blood serum levels of 20 to 40 micrograms per ml. and concomitant spinal fluid levels of 10 to 20 micrograms per ml. when two injections of 50 mg. per Kg. of body weight of the intramuscular preparation were administered at a twelve-hour interval. The blood and spinal fluid were obtained for assay twelve hours after the second dose. In these cases of meningitis treated with intramuscular chloramphenicol in a dosage of 50 mg. per Kg. every twelve hours, blood serum levels of 20 to 40 micrograms per ml. were maintained and the spinal fluid levels were 50 per cent of the serum concentration (10 to 20 micrograms per ml.). The chloramphenicol was present in the serum within one hour after administration in a concentration of 20 micrograms per ml. and this concentration persisted as long as twelve hours. The intramuscular preparation has been found to be an extremely useful and effective agent in infants and children. Thirty patients acutely ill with pneumococcal pneumonia, typhoid fever, Friedländer bacillus pneumonia with persistent bacteremia, subphrenic abscess, peritonitis, in addition to these cases of H. influenzae meningitis, have been treated with beneficial response.

The sensitivity of H. influenzae to the various antibiotics was determined. The results with twenty-two strains obtained from the blood or spinal fluid are summarized in Table III. No differences were noted when organisms isolated from the spinal fluid or blood were compared.

The penicillin sensitivities were often beyond the range ordinarily attained in the spinal fluid with parenteral administration. The spinal fluid levels of aureomycin in other bacterial meningitis studied have not been found to exceed 1 microgram per ml. even in the presence of acute inflammation. The inaccuracy of the biologic estimation of this antibiotic is well known. Terramycin has not been detected in significant amounts in the normal spinal fluid when administered orally. Streptomycin has been therapeutically useful although its concentration in the spinal fluid is low unless administered intrathecally. Polymyxin is too toxic for general use. Chloramphenicol was detected in the spinal fluid in concentrations exceeding the sensitivity of the most resistant strains in this series.

COMMENTS

Comparison of our data with other series is difficult in a disease such as H. influenzae meningitis because of the numerous inherent variables in each group. In a series treated with streptomycin and sulfadiazine between 1946 and 1949 a mortality of 3.4 per cent was reported. Sequelae observed were deafness (4.4 per cent), impairment of vision (4.4 per cent) and paralysis (1.0 per cent). Crook et al. have described their experience at the Harriet Lane Home of the Johns Hopkins Hospital from 1941 to 1948. These patients received sulfadiazine, streptomycin, specific rabbit antiserum and penicillin in various combinations. A total of forty-three patients were treated of whom sixteen (37 per cent) died and eight (16 per cent) recovered with evidence of residual significant brain damage. Among the children under one year of age the mortality was 46 per cent, as compared with 20 per cent among the older patients. Residual brain damage was noted among five of the twelve patients over one year of age who survived. In this series of thirty patients treated at the same institution between 1949 and 1951 there were two deaths from meningitis and one child died during convalescence unassociated with the meningeal infection. Among the nineteen patients in the group under one year of age only one death occurred (5 per cent). Residual neurologic damage was present temporarily in seven patients, or 26.0 per cent of the twenty-seven patients who survived. Evidence of impairment was still present at follow-up examination in five patients, or 15 per cent. No complications or residua were noted in the nine patients over one year of age who survived.

No statistical inference as to the superiority of chloramphenicol over aureomycin plus sulfadiazine can be drawn from this series. The low mortality and small series preclude such comparison. In the group treated with aureomycin plus sulfadiazine fourteen of a total of eighteen patients (78 per cent) were under one year of age, while only five (42 per cent) of the chloramphenicol group were in this category. Spinal fluid cultures, however, became negative in 66 per cent of the chloramphenicol group within forty-eight hours after initiation of treatment and in all by seventy-two hours. In the aureomycin group the spinal fluid of only 39 per cent and 78 per cent became sterile within forty-eight and seventy-two hours, respectively. It would appear that the ease with which intramuscular chloramphenicol can be administered (when the parenteral route is necessary), the resulting reproducible and maintained blood and spinal fluid levels, as well as the effectiveness of this antibiotic when employed without adjuvent therapy, are distinct advantages. A total of thirty-nine patients with H. influenzae meningitis treated with chloramphenicol has been reported without a single death.[13,14]

No evidence of hematopoietic, renal or hepatic toxicity was observed in this series of patients or in a larger group of infections which have been treated with aureomycin or chloramphenicol during the past two years. Three patients developed transient hematuria from the sulfadiazine which promptly subsided when the dosage was reduced or the sulfonamide therapy was discontinued.

At present there does not appear to be any indication for the use of specific rabbit antiserum, with its attendant reactions. In this hospital the results observed with aureomycin* or chloramphenicol are as satisfactory as or even superior to those obtained with streptomycin.

SUMMARY

Thirty children with bacteriologically confirmed meningitis due to H. influenzae type b have been treated with aureomycin and sulfadiazine or with chloramphenicol.

Eighteen patients received intravenous and

* The aureomycin was kindly supplied by the Lederle Laboratories Division, American Cyanamid Company. Chloramphenicol was made available by Parke, Davis and Company.

oral aureomycin supplemented by parenteral and oral sulfadiazine. There were three deaths among these eighteen patients of which two could be attributed to the infection. Some residual neurologic damage was observed in five patients.

Twelve patients received oral, intramuscular or intravenous chloramphenicol therapy No deaths occurred and only two patients showed residual neurologic disturbances.

The neurologic complications diminished considerably several months later in four of the seven patients.

Because of the difference in age selection between the two groups, no distinction between the two types of therapy can be made with any assurance. Chloramphenicol appeared to possess certain advantages in the clinical care of these acutely ill children, many of whom were infants. No toxic manifestations which could be attributed to the medication were encountered among any of the patients in this series.

Subdural collections of fluid were often observed and the importance of recognizing this complication is re-emphasized.

Acknowledgment: We wish to thank Dr. Harold E. Harrison and Dr. Lawrence Finberg of the Pediatric Division of the Baltimore City Hospitals for their aid and cooperation. Elizabeth Gault Fisher, PH.D., Bacteriologist at the Harriet Lane Home, the Johns Hopkins Hospital, isolated and typed the organisms from these patients. Drs. Paul Hardy, John F. Crigler and the House Staff at the Harriet Lane Home, The Johns Hopkins Hospital, contributed much to the clinical care and execution of this study.

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Diagnosis and Immediate Prognosis of Japanese B Encephalitis*

Observations Based on More Than 200 Patients with Detailed Analysis of 65 Serologically Confirmed Cases

LT. COL. ROBERT B. DICKERSON, M.C., MAJ. JOSEPH R. NEWTON, M.C. *and* CAPT. JAMES E. HANSEN, M.C.

San Francisco, California

With the onset of the Korean conflict many new medical challenges were anticipated. By the end of 1950, however, the only entity to reach significant proportions, among those diseases not regularly encountered in the United States, was Japanese B encephalitis, hereinafter referred to as JBE for the sake of brevity. Previously, JBE became an American military problem during a small epidemic on Okinawa in 1945.[1] Since that time it has remained a small but annual medical challenge to our forces in the orient.

JBE is a specific viral encephalitis occurring throughout Japan and parts of Asia annually in the late summer and early fall. It was originally given the designation "B" to distinguish it from Von Economo's disease, known generally as type A encephalitis. Transmission is by the mosquito and the members of the Culex genus are probably the most important offenders.[2,3] In endemic areas many animals can be demonstrated to act as reservoirs of infection. These range from mice to large farm animals.[4] In addition, a large proportion of the indigenous population is found to have immunologic evidence of the disease. The demonstrable serologic response to JBE is the development of specific complement fixing and neutralization antibodies. Immunization procedures have been carried out with injection of chick embryo and mouse brain vaccines.[5,6]

In Korea thousands of American soldiers were thrown into combat situations which precluded measures to protect against mosquitos or other potential arthropod vectors. They were subjected to nutritional privation and maximal physical stress. All this occurred in a country known to have a high endemic rate of JBE.[7] Largely as a result of this hazardous situation 299 soldiers developed the disease diagnosed clinically as JBE during the months of July to October, 1950. There were thirty fatalities among this group, an over-all mortality rate of 10 per cent. All of these cases originated in Korea.[9] Barring immediate fatality, these patients were evacuated to fixed hospitals in Japan and 228 of them were seen by the authors at the 118th Station Hospital. It was during the month of September that successful military operations permitted slower movement of the evacuation chain. That circumstance, plus the cooperation of the 361st Station Hospital, provided the opportunity for a minimum of eight and an average of ten weeks' observation of 110 patients who were hospitalized thereafter.

CASE SELECTION

Although these last 110 cases were clinically a homogeneous entity, subsequent serologic determinations yielded diagnostic complement fixation reactions in only sixty-five. An additional thirty cases demonstrated antibodies which were not of sufficient titer to be considered diagnostic of JBE. The remaining fifteen cases failed to develop specific antibodies. These serologic procedures were performed at the 406th Medical General Laboratory where a titer is adjudged to be diagnostic if it undergoes a four-fold rise, and confirmatory if positive at 1:16 dilution. These criteria conform to the generally accepted standards for the serodiagnosis of JBE.[6,10]

* From the Medical Service, 118th Station Hospital.

It is the belief of the authors that the bulk of the cases without serologic confirmation actually were due to JBE. The clinical picture was unvarying within the group as a whole, and as a group these cases stand out sharply from the remainder of the central nervous system diseases

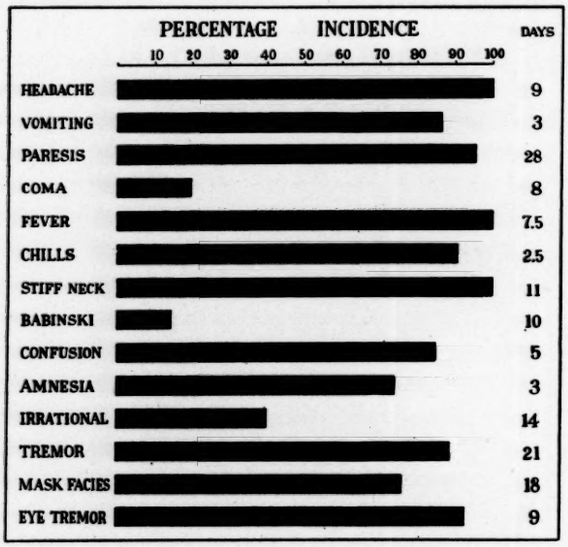

FIG. 1. Percentage incidence. Several significant signs and symptoms are listed together with the time of their average duration.

seen in the Far East Theatre. This observation is consistent with previous reports of JBE epidemics wherein serologic confirmation was by no means invariable.[7,8] Although technical problems such as refrigeration probably interfered in these series, there has nevertheless remained a significant proportion of cases without such confirmation. Neutralization tests would probably have established the diagnosis in additional cases. However, neutralization determinations are very difficult to perform, and their interpretation is often equivocal.

In order to avoid any such problems the statistical data presented here are based upon detailed observation of the sixty-five proven cases. However, the findings in the proven group closely parallel those seen in the epidemic as a whole. The picture of these sixty-five patients is an accurate reflection of JBE as seen in 1950.

HISTORY

The *onset* of JBE was seen to be rapid but not sudden. There was a two- to four-day interval between the initial symptom of illness and the development of full-blown meningeal signs. During this initial prodromal period headache and fever were the prominent findings, and a definite diagnosis could not be made clinically. The presence of severe chills suggested malaria or pneumonia, and one-fourth of these patients were diagnosed as such. Many were labelled as combat fatigue because of their confusion. Nuchal rigidity was occasionally present early and, when recognized, was an invaluable aid to diagnosis. Sore throat was rare.

The *presenting symptom* was headache in 80 per cent of cases. Others sought aid for chills, fever, nausea, vomiting, dizziness, sore legs and drowsiness. In two cases the disease was ushered in by grand mal seizures. Convulsive phenomena were the exception, however, and were present in only five of the cases at any time. Figure 1 illustrates statistically the incidence and duration of many of the important findings of JBE.

Headache represented a common denominator of the series, being present in all cases. The severity was attested to by its predominance as a chief complaint. Our appraisal of intensity was recorded as severe or very severe in 81 per cent. The character of the pain followed no consistent pattern but the location was frontal or generalized in nine-tenths of cases. Unilateral or occipital localization was exceptional. Analgesic agents offered little benefit. Headache persisted for nine days and remained severe or moderately severe throughout this time. The relief with defervescence was not always constant, and one-third of the patients continued to note intermittent mild headache for two months.

Fever was always present and lasted for slightly more than one week. The temperature usually rose above 104°F., reaching its peak in two to four days and subsiding gradually over a five-day period. It was not significantly influenced by antipyretic agents. The curve itself showed little daily fluctuation.

Chills are not unusual for any disease characterized by a marked febrile response, but they have been especially striking in JBE. Nine-tenths of the patients noted chills. These were accompanied by shaking and were of such severity that the patient often underwent a therapeutic trial for malaria. Although the temperature elevation was not remitting, the chills recurred for more than two days.

Nuchal rigidity was present on examination in all cases. Nevertheless, it was not often of sufficient severity to concern the patient. In no case was it the presenting complaint. Half of the

patients did not recall having stiffness or pain of the neck. Only a few regarded their symptoms as being more than moderate in this respect. Lumbar backache likewise was not impressive in severity but it was noted regularly.

Vomiting was present in a high percentage and was usually accompanied by nausea. When this subsided after two to four days, it was followed by severe anorexia. The impairment of appetite persisted for two weeks. This of course played a role in the etiology of the associated emaciation and debility. It is to be noted, however, that the initial weight loss was not perceptibly decreased by early institution of gavage feeding. Many of these patients had mild diarrhea. Although the concurrent incidence of diarrhea in Korea was high, we believe that mild diarrhea represents a fairly frequent manifestation of JBE. The lack of constipation and fecal impaction in these prolongedly stuporous patients was in itself an unusual feature.

PHYSICAL FINDINGS

Alterations of *vital signs* were of a non-specific nature. Respirations were usually irregular in the seriously ill patient, but ventilation and oxygenation were adequate during the early stages. Only when pulmonary congestion and bronchopneumonia developed would cyanosis supervene. Cardiovascular abnormalities generally corresponded to the duration and degree of the hyperpyrexia. Although a relative bradycardia has been noted by others, this was seen in only four of our patients. Marked flushing of the face and supraclavicular areas was frequent. In contrast to bulbar poliomyelitis, hypertension was not observed.[11]

The *facies* can be described as dull, flat, staring and mask-like. The common factor to all was a lack of facial mobility and expression indistinguishable from that of chronic Parkinsonism. The palpebral angle was wide and the rate of blinking diminished. This was striking in half of the patients and noticeable in another quarter. During the febrile period the blank expression was frequently punctuated by bizarre grimacing. The usual duration of this facial appearance was nearly three weeks. Although they were undergoing improvement, five patients continued to present an abnormal appearance at ten weeks. Three patients showed a broad margin of visible sclera both above and below the iris.

Frank *cranial nerve* paralyses were evident in only five instances, but more subtle cranial nerve aberrations were very common. There were no instances of blindness or visual scotomas. In several cases there was mild blurring of the optic discs but frank papilledema was not encountered. Diplopia and blurring of vision were not infrequent but clinically apparent weakness of the extraocular muscles could be demonstrated only once. The most notable ocular manifestation was tremulous eye motion by a series of shuttling movements. Normal movement was restored soon in the post-febrile state. No nystagmus was seen. Miosis and sluggish light responses were present in most instances. These were often accompanied by conjunctival hyperemia and photophobia.

Three patients developed frank unilateral facial paralysis. In each case the orbicularis oculi and upper facial muscles were involved to the same degree as the lower facial muscles. After eight weeks this weakness persisted in each case but was undergoing improvement. Mild facial weakness, on the other hand, was very common, and was most frequently manifested as weakness in maintaining frontalis contraction and inability to "show your teeth." Minor degrees of facial asymmetry were frequently discernible.

There was no evidence of auditory, vestibular or trigeminal involvement other than absent corneal responses in deeply comatose patients. Nasal voice and nasal regurgitation did not occur. Glossopharyngeal or vagal weakness occurred only as a manifestation of generalized paresis or stupor, and this was made apparent as a thick-tongued speech. Sternomastoid weakness was a marked feature of the generalized paresis but no localized involvement could be ascribed to the spinal accessory or hypoglossal nerves.

Generalized paresis was a constant feature of the disease. The patient was weak before he was hospitalized in most instances, but the maximum weakness was not reached until the fifth or sixth day of the disease. By this time the patient had usually begun to improve in terms of temperature. Although the weakness was a general process, it was most intense in the flexors of the neck. It bore no apparent relationship to the nuchal rigidity. Generalized paresis held the average patient bedfast for seventeen days, and it was four weeks before he regained sufficient strength to attempt any form of ward duty. This paresis was unaccompanied by apparent

muscular atrophy or flaccidity. There was muscle shortening and increased resistance to stretch in more than half of the cases. The tendon reflexes were usually brisk or hyperactive without clonus.

Localized paresis was present in 31 per cent of the cases, about half of which had localization at more than one site. Upper extremity involvement was predominant, being almost three times as frequent as lower extremity weakness. It often appeared in the guise of a late manifestation because it was accentuated when the general strength returned to sufficient degree to provide a contrast. Three patients demonstrated lower motor neuron involvement, and each had these characteristics in common: (1) There was definite local atrophy; (2) the reflexes in the area involved were hypoactive or absent; (3) muscle tonus was decreased; (4) the weakness was sharply localized to specific muscle groups and confined to a small area anatomically and (5) there was little tendency to improvement of these findings after twelve weeks.

Localized paresis of upper motor neuron origin presented very different findings. There was no atrophy or flaccidity. The muscle tonus in the involved areas was increased in the acute phase, but normal tonus tended to return as the fever subsided. The deep tendon reflexes were not asymmetrically hypoactive. The paresis, although marked, was not extreme, and the involved muscle could counter the force of gravity. The weakness was not sharply localized and large areas were involved. Usually an entire extremity showed a relatively uniform degree of weakness. This type of paresis was five times as frequent as lower motor neuron involvement, being seen in 26 per cent of cases. There was rapid improvement. At the time of discharge residua of this type were evident in only three cases.

The typical *posture* for the severe case of encephalitis was that of flexion of the upper extremities and extension of the lower extremities with pes cavus. This corresponds to the posture of decorticate rigidity. The position of the hands and feet was in keeping with the descriptive term of carpopedal spasm. However, repeated chemical determinations failed to establish the metabolic alterations implied by the latter term. With mental clearing this posture disappeared but not the hypertonus of the biceps humeri and pes cavus. The feet became normal when the patient was again ambulatory. The biceps shortening was slower to respond, and eight weeks after onset about one-fifth of the patients still complained of tightness or limitation of joint motion at the elbow. This was unrelated to sites of administration of intravenous fluids. Limitation was extensive enough to require prolonged physiotherapy in six instances.

Muscular rigidity was seen in over 40 per cent of the cases and was a strong diagnostic point in favor of encephalitis. It was best demonstrated by passive flexion of the elbow. There was often a "cog-wheel" component present but this was never striking. Other frequent muscular manifestations were myoclonic twitches and myotonia.

Incoordination of mild degree was present in half of the patients. This was most marked in those extremities in which upper motor neuron involvement was present. It subsided rapidly, and at three weeks time only a few continued to have difficulty as measured by tests of digital agility. No true ataxia was demonstrated.

Tremor of abnormal degree as shown in Figure 1 was present in almost 90 per cent of the patients. It was moderately coarse in nature and was accentuated by fatigue and fine purposive movements. Patients with tremor at one site at times had none elsewhere. The most important sites for this manifestation were the fingers, the tongue and the closed eyelids. The average duration of tremor was three weeks. At a time when these patients were otherwise well enough to feed themselves, one-quarter of them were unable to hold a cup without spilling the contents. After ten weeks only 10 per cent of patients continued to have gross tremor. This is interpreted to indicate that the tremor was the result of the disease rather than a manifestation of inherent instability.

During convalescence the *gait* was abnormal in one-third of the patients. They walked stiffly, staring straight ahead with arms hanging immobily. Occasionally this loss of associated movement was unilateral. This abnormality disappeared before four weeks except in a few cases showing persistent mental derangement.

Sensory manifestations were ordinarily not detected during the acute phase of JBE. This was largely because of the confusion of the patient but also due to the type of sensory disturbance encountered. As the patient regained his mental clarity he often brought to the physician's attention a "numb place." This site was found to consist of a well demarcated area which was described as being asleep. He stated

either that he felt nothing there, or that things felt strange when they touched the skin. Upon neurologic examination impairment was demonstrated in fields of pain, temperature, light touch and sharp-dull discrimination, yet there was never complete absence of the modalities. Obviously the disturbance was more striking to the patient than to the examiner. Still one could not fail to be impressed by the constancy of the findings in the individual case as well as the uniformity of the pattern in the group as a whole. These hypesthetic and paresthetic areas conformed to segmental dermatomes. This type of sensory disturbance was found in eight cases and persisted in each instance for a minimum of eight weeks. Improvement occurred in each case, with concentric diminution of the involved area.

Psychiatric deviation or disturbance of mental functioning was a characteristic finding of JBE. This most commonly manifested itself as confusion. Only ten patients failed to have severe confusion during the acute disease. In 72 per cent of the cases the confusion was of sufficient degree to result in amnesia for a portion of the disease course. The amnesia was often retrograde in nature. Forty-one per cent of the patients became irrational and disoriented and 20 per cent became completely comatose. Usually these aberrations would abate with the declining temperature. Less dramatic mental changes were present in almost all cases. The typical patient demonstrated uniform lethargy and apathy. He would stare blankly into space, accepting his meal in silence with little recollection of what he had eaten. There was no effort to read or otherwise remain occupied. By three weeks the patient had only minimal recent memory defects and began to seek about for pleasures and comforts. Although spontaneity had begun to return, his attention span was still markedly decreased. By four weeks time the patient was essentially normal mentally. Certain patients deviated dramatically from this pattern and presented frank psychotic manifestations in the post-febrile period.

Weight loss was the most remarkable finding in JBE patients outside the realm of the central nervous system. This occurred in even the mildest of cases and represented an average loss of 26 pounds or 16 per cent of the body weight. Although a portion of the decrement was due to combat life *per se*, a nearly equal loss occurred in patients who first manifested their disease after return to Japan. The low point of the weight curve was reached between one and two weeks after onset. The more severely ill patients continued to lose weight after the temperature returned to normal. During convalescence there was an average gain of 2 pounds per week.

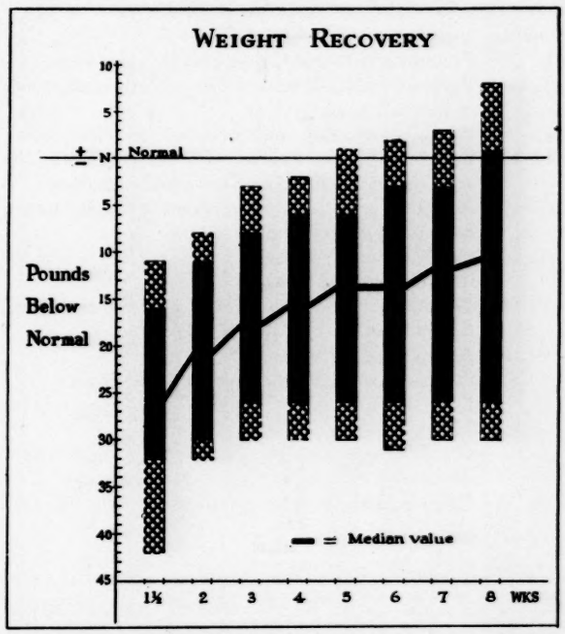

FIG. 2. Weight recovery. The weekly weight recovery of 65 sero-diagnosed cases of Japanese B encephalitis compared to their normal. Two thirds of the determinations at each given time period are represented by the solid black area. The cross-hatched areas include all but the upper 5 per cent and the lower 5 per cent of values.

Figure 2 demonstrates graphically the course of weight recovery. At the end of eight weeks only one-fifth of the patients had regained their normal weight. Half of them weighed 10 pounds less, and one-quarter of them weighed 20 pounds less than their norms.

RESIDUA

A survey of the disease residua ten weeks after onset revealed twelve of sixty-five patients with significant impediments to normal function. Each is listed in Table I.

Excluding this group which had obviously not recovered at ten weeks, the remaining patients showed a striking tendency for improvement. To those who saw them in the early phases it was almost inconceivable that so many gravely ill patients would make complete recoveries. Two of the above patients (E. D. and E. L.) made abrupt recoveries during the third month

of the disease. This justifiably raises the possibility of still later recovery of those patients psychotic at the end of twelve weeks' observation. Each of the latter demonstrated electroencephalographic abnormality.

TABLE I

PATIENTS WITH IMPORTANT RESIDUA AT TEN WEEKS

Patients	Residua
E. C.	Psychosis with confusion and deterioration
J. D.	Psychosis with deterioration, delusions and loss of moral values
E. D.	Psychosis abating with residual disorientation
H. H.	Left hemiplegia, flaccid paralysis of left tibialis anticus, hypophrenia of uncertain etiology
C. H.	Atrophy of intrinsic muscles of left hand, associated hypesthesia
E. L.	Confusion and lack of moral values (markedly improved at 12 weeks)
P. M.	Psychotic with disorientation, deterioration, emaciation and left facial palsy
W. P.	Atrophy of right serratus anterior
E. S.	Psychosis with deterioration and delusions
H. T.	Left facial palsy (markedly improved at 12 weeks)
J. W.	Confusion and weakness of entire right upper extremity (much improved at 12 weeks)
R. Y.	Marked intellectual impairment and general debility

The greatest toll was seen as mental and psychiatric damage. At the end of three months' observation five patients were still completely incapacitated in these spheres. Motor impairment of significance was seen in three patients at three months. Each of these patients demonstrated lesions of lower motor neuron type. Patient H. H. had also a left hemiplegia. This was the only instance of upper motor neuron involvement persisting for three months.

Intellectual impairment and confusion characterized those patients who became psychotic. All had delusions but hallucinations were not noted. One patient had illusions, and two were aggressively antisocial. While masturbatory activity was commonly observed in the phase of acute irrationality, in the post-febrile stage public masturbation was practiced by only two patients, one of whom also made open homosexual advances. During the first afebrile week two of the psychotic patients demonstrated definite improvement, only to relapse into frank psychosis. (One fatal case also showed brief remarkable improvement in the immediate post-febrile period.)

Army classification battery tests are given routinely to all enlisted men at the time of their entry into military service. Thus by repeating these tests the opportunity was afforded to compare the abilities of the patients with their achievements in the past. Comparative scores were available for thirty-six patients. The results in these patients were confirmatory of the clinical impressions already drawn. Generally those patients without gross evidence of mental deterioration did not show significant deviations from their previous scores.

PROGNOSIS

The clinical and laboratory findings of the most severe cases have been carefully reviewed to determine which factors in the early course of the disease were indicative of a more grave outlook.

The presence of a positive Babinski sign was a serious prognostic indication. It was found in only one case which did not have residua or fatal termination. Likewise the prolongation of fever was an unfavorable factor. All patients febrile for eleven days or more had residua or fatal termination. Two-thirds of the cases with albuminuria during the acute stage demonstrated residua at eight weeks, and virtually all fatal cases had albuminuria at some time.

The spinal fluid provided certain prognostic correlates. Although the cell count bore no direct relationship to the course of the disease, both patients with more than 1,000 cells per cu. mm. developed severe residua. On the other hand, a low cell count did not insure a mild course. There was no correlation of disease severity with the percentage of polymorphonuclears in the spinal fluid. Initially the protein level was uniformly elevated as seen in Figure 3. During the second month those patients with disease residua had protein levels which averaged 30 mg. per cent higher than the group as a whole. Although this is interesting in respect to pathogenesis, it can hardly be considered of prognostic value.

The blood findings, including the titer of JBE complement fixing antibodies, showed no significant correlation with disease severity.

LABORATORY STUDIES

The attention was focused primarily upon the findings of lumbar puncture, and justly so. In all cases there was an abnormal number of cells present in the cerebrospinal fluid. The results of approximately 500 serial lumbar punctures are presented in Figure 3. Ninety per cent of initial cell counts ranged between 20 and 400 per cu. mm., averaging 185. Two cases had cell

counts in excess of 1,000. There was a marked persistence of pleocytosis, and virtually all counts remained abnormally elevated throughout seven weeks of follow-up. The character of the cellular response observed varied with the tween 40 and 100, the more severe cases presenting the higher levels. Even at nine weeks almost half of the cases continued to have levels in excess of 40 mg. per cent. Three cases had protein levels in excess of 125, the highest being

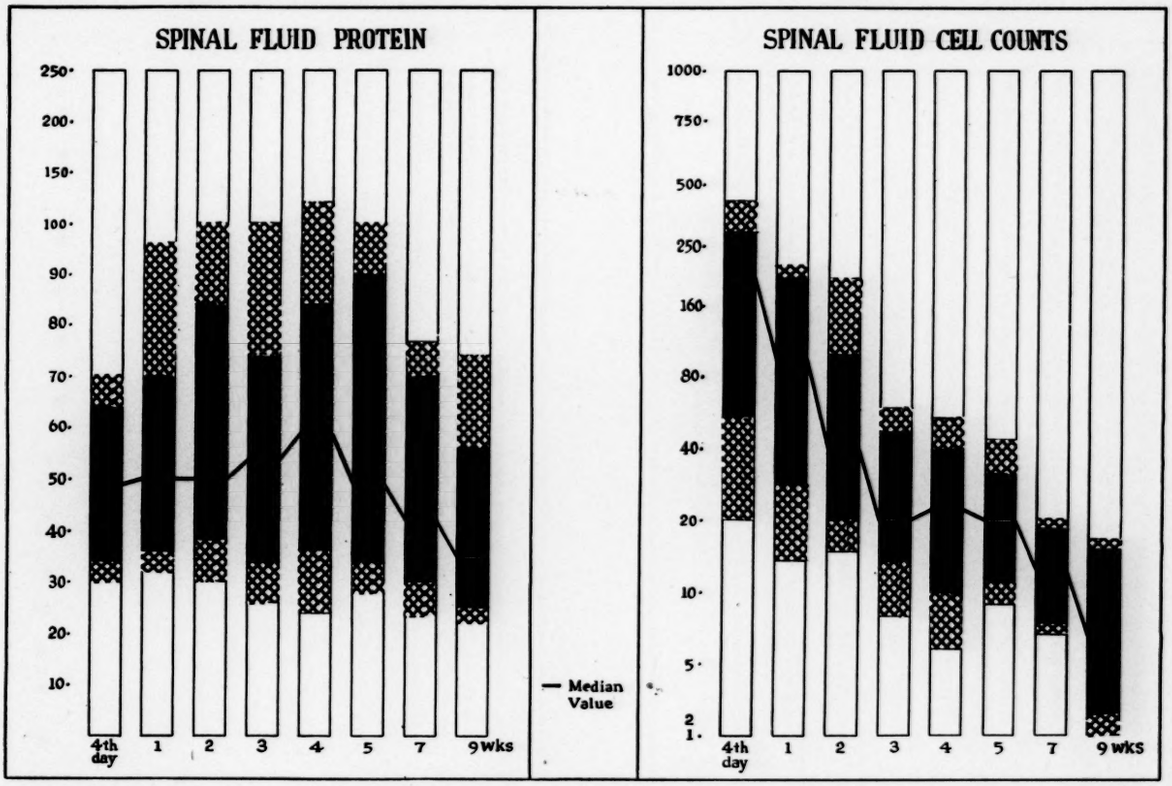

FIG. 3. Spinal fluid protein and spinal fluid cell counts. Two-thirds of the determinations at each given time period fell within the solid black area. The cross-hatched areas include all but the upper 5 per cent and the lower 5 per cent of values.

time of lumbar puncture. During the first four days of illness approximately one-third of the cells were polymorphonuclears. Very rarely did the percentage of polymorphonuclears exceed 80. Conversely, no fluid revealed all lymphocytes during the first four days. By the end of the first week of disease the percentage of polymorphonuclears dropped markedly to a median of 6. Still there were few cases which had only lymphocytes. Following the first week polymorphonuclears were found infrequently.

Chemical examination of the cerebrospinal fluid revealed abnormality only of the protein content. Chloride and sugar levels were not influenced by the disease. Initial examination demonstrated a moderately elevated protein level, being above 45 mg. per cent in 70 per cent of the cases. For the ensuing seven weeks there was little change. The levels remained be-

250. Spinal fluid pressure lay within the high normal range, rarely exceeding 250 mm.

The significant hematologic data are presented in Figure 4. There was an initial leukocytosis of moderate degree, with the usual count being from 10,000 to 19,000. A few counts were normal and a few ranged from 20,000 to 30,000. No leukopenia was present. The response was brief, and by the end of the first week the average count was 10,000. Minimal elevation of the leukocyte count persisted until the fourth week in most cases. The leukocytosis was paralleled by a moderate neutrophilia. The average initial percentage of polymorphonuclears was 78 per cent. This dropped to 65 per cent at the end of two weeks. The erythrocyte sedimentation rate was uniformly elevated, reaching an average of 35 mm./hr. (Wintrobe corrected) at the end of the first week. Thereafter there was a steady

decline. Most cases became normal by the fourth week.

The development of specific complement-fixing antibodies is a late occurrence. As can be seen from Figure 5, one-third of the diagnostic

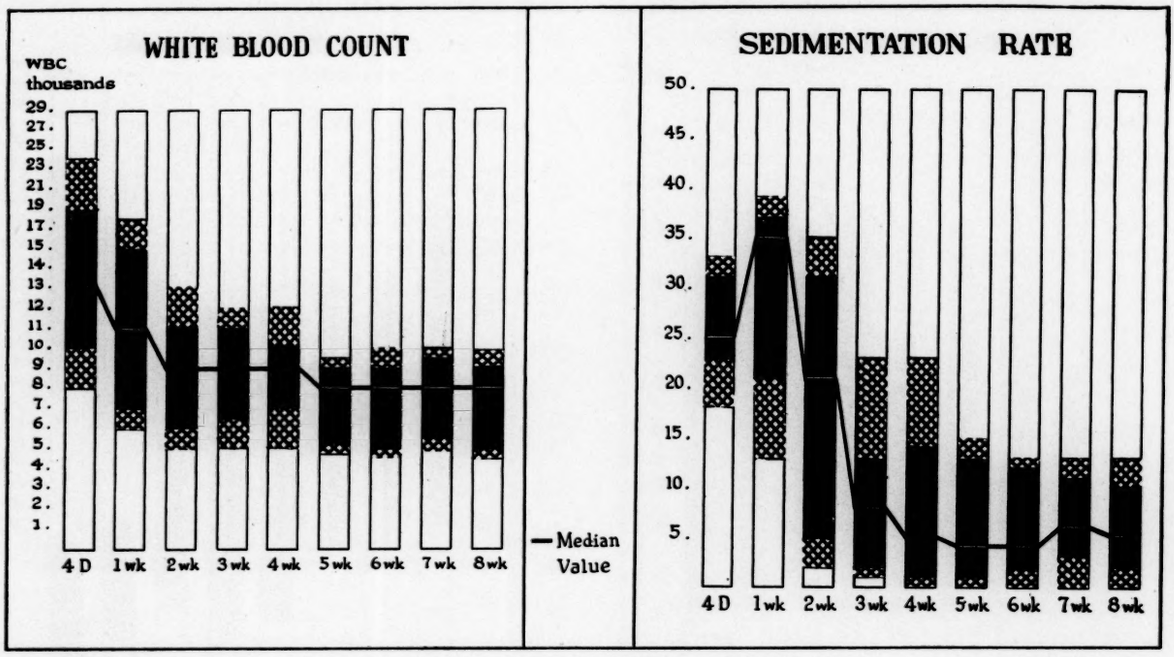

FIG. 4. White blood count and sedimentation rate. Two-thirds of the determinations at each given time period fell within the solid black area. The cross-hatched areas include all but the upper 5 per cent and the lower 5 per cent of values.

titers developed more than a month after the onset. At the end of three weeks only one-fifth of the cases had developed diagnostic levels. It is to be noted that three weeks has been regarded by some as the optimal time for final serum collection. This emphasizes the importance of paired sera for comparison. It stresses even more the necessity of drawing a specimen late in the phase of convalescence. Six weeks should represent the minimum time for serologic follow-up unless the diagnosis has been previously established. There was no significant descent in level of complement-fixation antibodies in the first eight weeks.

DIFFERENTIAL DIAGNOSIS AND COMMENTS

An effort has been made to emphasize that JBE, as represented by the serologically confirmed cases described, is a clear-cut clinical entity. This emphasis arises from the relative ease with which other concurrent febrile central nervous system (CNS) states could be differentiated. Soon after the outset of this epidemic it was recognized that the various cases of JBE differed basically only in the quantitative severity of the disease. Many features were of such constancy that the encephalitic syndrome encountered could be diagnosed on the basis of positive findings and not by the process of excluding all other entities.

For all practical purposes, the onset of the invariable headache marks the beginning of significant symptoms. Careful examination and history taking readily give indication of nervous system pathosis. If one is alerted to this possibility, the presence of a CNS lesion is directly confirmed by the presence of a spinal fluid pleocytosis. The character of the cellular response, plus the absence of bacteria or chemical alteration, serves to delineate the condition as a non-bacterial CNS infection. Within this group further identification must be made by means of physical diagnosis and serologic studies. Unfortunately the latter is of only retrospective value, and one must rely on physical findings in any case under direct consideration.

On the basis of relatively characteristic findings a "JBE syndrome" may be identified. It is not implied that absolute identification can be made in this respect. Certainly equine encephalitis, St. Louis encephalitis and encephalitis

lethargica may present identical features. Yet by careful scrutiny the diagnosis may be limited to a small group of acute viral encephalitides.

The most significant findings on physical examination may be reduced to 6 in number, of which the presence of 4 can probably be regarded as pathognomonic of the "JBE syndrome." They are: (1) Altered sensorium; (2) mask-like facies; (3) "thick" slow speech; (4) coarse ocular tremor; (5) relatively symmetrical neurogenic paresis without corresponding sensory lesions or paralysis and (6) normal or increased deep tendon reflexes and/or abdominal reflexes, barring profound depression of vital functions.

1. The most apparent feature of the disease is the altered sensorium which the acutely ill patient exhibits. Still more remarkable is the fact that the alteration in sensorium is primarily of the same nature and direction in all patients, with individual differences mainly in the severity of the alteration. Thus the presenting picture betokens a varying degree of retardation and flattening of affect. The typical patient is quiet and uncomplaining and, unlike the poliomyelitis victim, not apprehensive. By the same token, it is difficult to arouse either his approval or disapproval. During the obviously irrational or comatose state which often supervened following admission the same basic pattern of personality inertia persisted.

2. In the experience of the authors, no disease other than chronic Parkinsonism has so regularly produced a mask-like facies. In the patient who is severely ill, recognition of this facies is well nigh inescapable, with its unwinking gaze and expressionless appearance. This attitude is in sharp contrast to the apprehensiveness and clear reacting mind seen in bulbar or spinal poliomyelitis. It should be emphasized that this facies disappears dramatically during recovery. One may be unable to recognize the patient a week later when the pathologic facies has disappeared.

3. The thick retarded speech is best imitated by trying to talk slowly with a minimum of movement of the tongue, as if with a "mouth full of mush." This sign points out a conspicuous difference between the delirium of JBE and other equally grave states. Although it may be garbled and senseless, the rate of speaking in other types of delirium is seldom as regularly altered. For example, in the anoxic ramblings of severe poliomyelitis the sounds which are vocalized are proportionately normal or nasal although weak. The meningitis patient may rave maniacally, while the delirious subarachnoid hemorrhage victim tends to talk quietly. In JBE, intelligible speech is slow, thick and without normal tonal inflection. Nasal speech and associated regurgitation, as seen typically in bulbar poliomyelitis, were not observed.

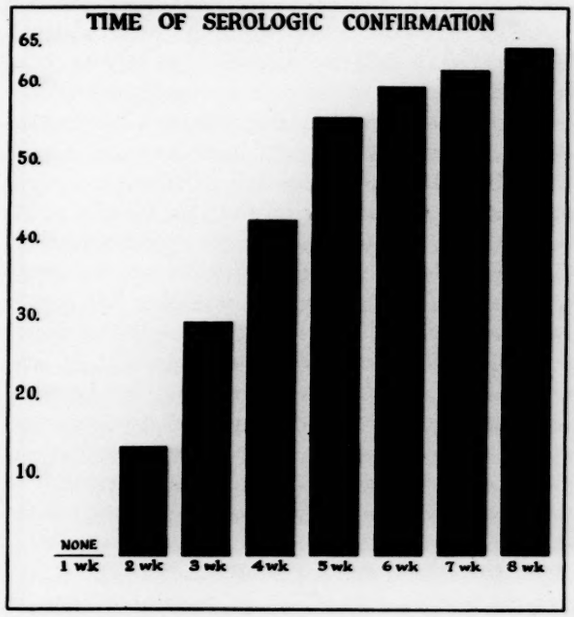

FIG. 5. Time of serologic confirmation. The columns indicate the weeks required before serological diagnosis was obtained in 65 sero-diagnosed cases of Japanese B encephalitis.

4. The presence of a coarse ocular tremor was of notable constancy in these cases whereas it has only rarely been observed in other types of febrile CNS disease. It is composed of two elements: One component is a "cogwheel" type of pursuit movement in following a moving object. Basically, it is an inability of the focused eyes to follow smoothly an object moved in the horizontal plane. The eyes pursue by performing a series of rapid distinct stops and starts in shuttling fashion. The occurrence of this phenomenon in encephalitic states has been pointed out by Savitsky.[12] The other component of the tremor is seen when the eyes are fixed upon a stationary object. There is a conjugate jerking of the eyes a few degrees to one side and then to the other of the object being focused upon. Loosely used, the term pseudo-nystagmoid might be applied but it is entirely inadequate to describe the global tremor observed. The rhythmical shift of the eyes with the fast and slow components implied by this term was not observed. The rate of the

ocular tremor was approximately equal to that of the lid tremor with which it was usually associated.

5. The relatively symmetrical neurogenic paresis without significant sensory alterations at the onset and without complete early paralysis was a virtually invariable finding which required interpretation only in assessing its severity. As such, it stood out in contrast to the asymmetrical defects of poliomyelitis, the sensory dysesthesias of post-infectious polyneuronitis and the localized abnormalities associated with intracerebral and basilar meningeal lesions. Essentially symmetrical facial nerve weakness was impressive. The typical patient slept with the sclerae conspicuously unlidded, and he was able to wrinkle his forehead only feebly. Although volitional control of the extremities was retained, it was enfeebled to a degree entirely out of keeping with the degree of toxicity and temperature elevation encountered. Very often the patient could do little more than counter the force of gravity. This is in contrast to the power and endurance so frequently encountered in the comparable stages of purulent meningitis. This paresis was more striking in the upper than in the lower extremities. No patient presented himself initially because of inability to use an extremity. Lower motor neuron involvement was never readily apparent during the first week of the disease. In contrast to poliomyelitis, actual paralysis was late in coming to the attention of the patient and doctor.

6. Other febrile CNS diseases associated with neurogenic paresis very rarely display hyperactive deep tendon reflexes and the superficial abdominal reflexes are not remarkable. In JBE the reverse is true. The degree of reflex activity covered a wide range, but three important differential points were observed. First, the responses were almost universally symmetrical and equal in all extremities. Second, there was no diminution of reflexes associated with localized or regional paresis. (This was not true for small areas in three patients having lower motor neuron involvement.) Third, the reflexes of the average patient were not depressed. About one-third of the patients demonstrated hyperreflexia. A second one-third had normal deep tendon reflexes. The remaining third had hyporeflexia. About half of the last group had absence of reflexes. This was usually associated with coma. The degree of activity of the deep tendon reflexes was seen to be sharply diminished by fatigue. Otherwise, rapid changes in reflex intensity were rarely observed.

Abdominal cutaneous reflexes were absent at some time in half of the patients. These usually returned as the fever subsided. In contrast, many instances of hyperactive abdominal reflexes were encountered. In these cases there was muscular contraction above the costal margin or below the inguinal ligament. It is of interest that this type of reaction is cited by Brock as indicative of extrapyramidal involvement.[13] The cremasteric response was never noted to be hyperactive. It was absent at some time in 65 per cent of cases. This absence persisted well into afebrility, and almost half of the cases presented active abdominal reflexes and absent cremasteric reflexes during the second week of the disease. As has been noted elsewhere, the occurrence of positive Babinski or other toe signs was surprisingly infrequent.[14]

Alterations of muscular tonus were exceedingly common and assumed many forms other than the familiar "spasticity." Tapping the biceps muscle would often elicit the phenomenon of myoedema.[15] This consisted of a transient tumefaction or palpable ridge about 1 cm. long, the direction of which was perpendicular to the long axis of the muscle stimulated. It disappeared in three to eight seconds. Myoclonic contractions were common, especially in the pectoral area. The tonus of the smooth muscle was likewise relatively increased, with virtual absence of constipation or abdominal distention, and frequent spasticity of the urinary bladder. The very commonly occurring urinary incontinence was not characterized by dribbling.

The clinical findings of JBE correlate well with the known pathology of the disease.[16,17] There is diffuse edema and congestion of the brain, meninges and usually of the spinal cord. This is accompanied microscopically by perivascular cuffing and infiltration of lymphocytes and a few polymorphonuclear cells. Widespread neuronophagia and necrosis is prominent in the substantia nigra, red nuclei, basal ganglia, cerebral cortex, cerebellar cortex, medulla and the horns of the spinal cord. Virtually any portion of the CNS may be involved; therefore, findings such as lower motor neuron paralyses and segmental hypesthesias can be rationally explained on the basis of the observed myelitic process. We know of no evidence of dorsal root ganglion involvement.

No final answer can be given at this time as

to the efficacy of JBE immunization procedures. Many patients who experienced the disease in a severe or fatal form had received the routine immunization. This does not indicate that the vaccine is not of complete or partial immunizing value in some instances. However, previous immunization guarantees neither protection nor attenuation.

Despite the lack of specific therapy for JBE the mortality incidence in our troops (10 per cent) was about one-third of that seen in the Japanese population.[18] The great bulk of this difference was explained by the supportive care given these patients throughout the theatre. Fluid replacement, gavage feeding and vitamins were important. Undoubtedly the most vital factor was maintenance of an adequate airway. This was often accomplished by proper positioning and use of a suction catheter. In more severe cases the use of endotracheal intubation was lifesaving. The intubation was accomplished by the nasal route without direct visualization. A large catheter was utilized to allow for tracheobronchial toilet as well as oxygen administration. In addition, the dead air space was minimized, a distinct advantage to the anoxic patient with shallow respirations. The only complication arising from the use of this method was one instance of mild unilateral laryngeal palsy in a patient who required intubation for over one week.

The immediate cause of death in those cases which terminated fatally was bronchopneumonia, pulmonary congestion and edema, and interference with pulmonary ventilation, rather than primary failure of the respiratory mechanism. Pulmonary congestion and infection were combatted by frequent changes of position, utilizing gravity to assist in tracheal drainage. The foot of the bed was elevated most of the time but the head was not maintained too long in dependent position without respite. Antibiotics were used prophylactically in severe cases.

SUMMARY

A review is presented of sixty-five cases of serodiagnosed Japanese B encephalitis. An attempt has been made to point out the nature and course of this disease, and to stress those factors which distinguish it as a clinical entity. Admittedly these findings incompletely differentiate Japanese B encephalitis from the remainder of the acute viral encephalitides but they constitute a readily recognized "encephalitis syndrome." The findings most characteristic of this syndrome are: (1) Altered sensorium, (2) mask-like facies, (3) "thick" slow speech, (4) coarse ocular tremor, (5) relatively symmetrical neurogenic paresis without corresponding sensory lesions or paralysis and (6) normal or increased deep tendon reflexes and/or abdominal reflexes, barring profound depression of vital functions.

The presence of four or more of these findings can probably be considered diagnostic of the Japanese B encephalitis syndrome.

The prognosis for life was 90 per cent. Of those surviving 7 per cent were mentally incapacitated at the end of three months. An additional 5 per cent had partially disabling paralyses. The majority of these latter cases were lower motor neuron in origin.

Certain laboratory features which have not been previously stressed are: (1) Spinal fluid pleocytosis persisting for more than seven weeks; (2) polymorphonuclear cells present in the spinal fluid in all cases examined during the first four days of the disease; (3) regular elevation of the sedimentation rate with a mean of 34 mm./hr. (Wintrobe corrected) and (4) slow development of specific complement-fixing antibodies so that diagnostic titers may not be reached for six weeks after onset.

Japanese B encephalitis is a disease of dramatic severity, requiring the utmost in nursing and medical care. Convalescence is slow and prolonged hospitalization is mandatory. Of those surviving, about 10 per cent can be expected to demonstrate serious sequelae at three months.

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Aureomycin in the Treatment of Systemic North American Blastomycosis*

LEON V. MCVAY, JR., M.D. *and* DAVID S. CARROLL, M.D.
Memphis, Tennessee

With the successive advent of the recent antibiotics and chemotherapeutic agents there has been a remarkable reduction in the morbidity and mortality of many common infectious diseases.[1] One notable exception to this therapeutic progress, however, has been systemic North American blastomycosis.

In the ten-year period ending June 1, 1951, eleven proven cases of this disease were observed at the John Gaston Hospital and the University of Tennessee College of Medicine. Despite intensive therapy nine of these patients died within 2.5 years after the onset of signs and symptoms of the systemic form of this infection. Two patients reported in this article received prolonged aureomycin therapy with encouraging clinical results.

That blastomycosis is probably much more common than is generally believed is borne out by the work of Martin and Smith who in 1939 reviewed the literature and collected 347 possible cases, with eighty of them proven.[2] This infection appears to be largely confined to North America, with cases reported from at least twenty-eight states. Proven cases have also occurred in Canada, England and Australia.[3,4] All of the patients observed at the John Gaston Hospital have been from Tennessee, Mississippi, and Arkansas.

North American blastomycosis, or Gilchrist's disease, was first described in 1894.[5,6] It is a specific, chronic infectious disease caused by a fungus, Blastomyces dermatitidis. This fungus assumes a variety of forms in culture depending upon the medium and the temperature. On Sabouraud's medium at room temperature it can be isolated easily from purulent material. In seven days to two weeks it appears as a downy to fluffy colony which initially is white but later becomes tan. On blood agar at 37°C. a brownish, waxy to smooth growth occurs.[7] In this type the yeast morphology is maintained while in the downy colony rather characteristic conidia are present. B. dermatitidis is a nonfermenter. When a loopfull of purulent exudate is mixed with 10 per cent sodium or potassium hydroxide, the organism may be observed microscopically as a doubly refractile, ovoid or round body with granular cytoplasm, usually 7 to 10 microns in diameter although often as large as 20 microns. In tissue sections the wall of the organism is sharply differentiated from the contents, which are somewhat shrunken by fixation and therefore pull away from the wall leaving a definite space. The fungi may be found in tissue specimens in large masses but often are mingled with leukocytes in abscesses or are scattered through granulation tissue or are phagocytized by giant cells.[3] Of practical importance is the fact that the pathogenicity of B. dermatitidis appears to be of fixed character since after years in an artificial medium this organism can still produce disease.[3]

The exact method of infection in blastomycosis is not known. However, it is generally believed that the fungus enters the body via the respiratory system or through an abraded skin area.[2,8,10] Several cases of direct transmission from man to man have been reported.[11,13] It is known that the disease occurs spontaneously in animals.[14] Although the occurrence of B. dermatitidis outside of the body is not definitely established, it is believed to occur as a saprophyte in soil or dead vegetation.[7,15]

Blastomycosis is diagnosed eight to nine times more frequently in men than in women.[2,16] In our group of sixteen cases only one was a female; thirteen were Negroes and three were white. This apparently increased susceptibility of

* From the Divisions of Medicine, Pathology and Bacteriology and the Department of Radiology, University of Tennessee College of Medicine and the John Gaston Hospital, Memphis, Tenn.

Negroes can probably be explained by the fact that they comprise approximately 85 per cent of the patients at the John Gaston Hospital. Blastomycosis is a disease primarily of the lower economic groups and is diagnosed most often in manual laborers and agricultural workers who live in unhygienic surroundings.[9,16,17] All of the patients with blastomycosis observed at the John Gaston Hospital were of the lowest economic group.

This infection involves all age groups, the earliest case reported occurring in a six month old infant and the oldest patient being seventy-six years of age.[18,19] In our series the youngest patient was two years and the oldest sixty-eight years of age. However, more than half of the reported cases of systemic blastomycosis occurred between the ages of twenty and forty years.[2] In our group the age range was from twenty-seven to sixty-eight years with the greatest number occurring in those from thirty-four to sixty years. The cutaneous form of the disease involves a much wider age group.[2]

Clinically, we recognize a cutaneous and a systemic type of blastomycosis. The former is the more common variety. It may involve any part of the body but most frequently occurs on exposed areas such as the face, hands, wrists or ankles, or in an area of the body which has been injured by abrasion. The skin lesions of cutaneous blastomycosis are characteristically single. Initially such a lesion occurs as a papular pustule which ruptures, develops a friable necrotic crust and gradually extends centrifugally. The central portion becomes covered with crust while miliary abscesses appear near the margin. Large lesions show central involution with the formation of a soft, pinkish, atrophic scar and may cover large portions of the body in a serpiginous manner. These lesions are relatively painless; fever and subjective symptoms are rare. Scarification, however, may result in extreme disfigurement.

Forty to 50 per cent of all cases of blastomycosis are probably of the systemic type.[16,20] The systemic variety may follow primary infection of the skin but in most instances a pulmonic focus is responsible for dissemination of the disease. Martin and Smith, after reviewing 347 cases of proven and presumptive cases of blastomycosis, stated that in 50 per cent of cases of the systemic type the first symptoms were referable to the respiratory tract; in 4 per cent the primary lesions followed an injury of some kind; in 19 per cent a skin lesion was first noted; and in 23 per cent the earliest symptom was a cutaneous nodule or abscess.[2] Of the eleven cases of systemic blastomycosis observed at the John Gaston Hospital over a ten-year period three had initial respiratory symptoms; eight were first observed because of cutaneous lesions. Eventually all eleven developed pulmonic involvement.

In the systemic form of blastomycosis the organism is disseminated by way of the blood stream and lymphatics. Direct extension also occurs. Most frequently involved are the lungs, larynx, bones, liver, kidney, spleen, genitals, serous membranes and the central nervous system. It must be emphasized, however, that no tissue in the body is immune.[2,8,21,24] In contrast to the cutaneous type of disease, skin abscesses in the systemic form occur most frequently on the unexposed portions of the body, such as the back, abdomen and thigh.[2]

The clinical syndrome depends on the organ or organs involved as well as on the degree of involvement. In approximately half of the cases the onset of systemic blastomycosis is associated with symptoms referable to the respiratory tract, such as cough, pain in the chest and dyspnea. Productive sputum may occur but is not a striking feature in the early phase of the disease. The usual clinical picture is that of a chronic debilitating illness running a progressive downhill course characterized by weakness, weight loss, fever and anemia.[2,9,10]

The cutaneous and systemic forms of this infection are both caused by the same fungus. A definite diagnosis in either type of blastomycosis can be made only by demonstrating B. dermatitidis upon direct microscopic examination or in culture.

As far as life is concerned, the prognosis in cutaneous blastomycosis is good. Although many cases are resistant and exacerbations are common, at least temporarily good results are obtained in the majority of instances with iodide and roentgen therapy.[2,3,8,9,16,25,28] Potassium iodide was first used by Gilchrist and since then has been used extensively in cutaneous blastomycosis with marked improvement in the majority of cases.[29] Iodide is often given intravenously in addition to oral potassium iodide.[30,32] Martin and Smith reported that iodides are actually harmful in cutaneous and systemic blastomycosis when administered to a patient who is allergic to the fungus.[2,33] According to

these investigators, if a patient is skin-tested and found to be hypersensitive, a gradual course of desensitization should be undertaken before iodides are administered. Arsphenamine has been employed in some cases with equivocal results.[19] Radium and curettage have been reported to be of value.[31] Among innumerable preparations suggested for use in cutaneous blastomycosis are copper sulfate,[35] carbon dioxide snow,[36] silver nitrate,[37] gentian violet,[38] sulfonamides,[39,40] cauterization,[41] curettement or local surgical excision.[2,15,16] General hygienic measures, adequate diet, supplementary vitamins and control of secondary infection appeared to be helpful in the five cases of cutaneous blastomycosis observed at the John Gaston Hospital.

The prognosis in systemic North American blastomycosis is grave. There is no specific or adequate treatment for this fatal condition[7,16] and the disseminated form of this disease extends slowly until death results.[3] Martin and Smith reported a mortality rate of 92 per cent in patients followed up for two years or longer.[2] Eleven patients with proven systemic blastomycosis were observed at the John Gaston Hospital in the past ten years; nine died within 2.5 years, the remaining two cases reported in this article, were treated by prolonged administration of oral aureomycin and still survive.

Potassium iodide has been used more extensively than any other agent in the treatment of systemic blastomycosis.[2] However, Hyde and Ricketts state, "In no instance yet recorded has the continued administration of the iodide of potassium conducted any case to a satisfactory recovery."[37] Martin and Smith believe that it is curative in some cases.[33] Roentgen therapy,[2,3] vaccines[42,43] and intravenous arsenicals[43,46] have not produced definite sustained improvement in the systemic infection. Noojin and Callaway tested seven sulfonamides against B. dermatitidis *in vitro* and found that concentrations necessary to affect the fungus were too high for clinical use except, perhaps, as applied locally to cutaneous lesions.[39,40] Sayer reported that the sulfonamides and penicillin are of no value in systemic blastomycosis.[47] Littman, Wicker and Warren found two strains of B. dermatitidis to be resistant to streptomycin and penicillin in concentrations up to 200 units per cc.[48] Negative results with penicillin were also reported by Foster and Woodruff[49] and by Keeney, Ajello and Lankford.[50]

In view of our successful treatment of actinomycosis with aureomycin,[51,52] we decided to investigate the effect of administration of aureomycin in systemic blastomycosis.

CASE REPORTS

CASE 1. A thirty-seven year old Negro farmer from Mississippi entered the John Gaston Hospital on December 2, 1949, because of marked secondary infection of chronic cutaneous facial lesions, vague chest pain, cough and low grade fever.

This patient was observed in the Dermatology Clinic of the John Gaston Hospital and the University of Tennessee College of Medicine on June 20, 1945. He reported that his illness had its onset in the Spring of 1943. At that time he noted a small, painless papule on the distal portion of the nose. After repeatedly traumatizing it with his finger a pustular lesion developed. This extended progressively to involve the entire face. Marked eversion of both upper eyelids resulted. On the initial visit to the clinic B. dermatitidis organisms were demonstrated and the diagnosis of blastomycosis was made. Since comprehensive clinical and radiologic studies revealed no evidence of visceral involvement, the diagnosis of cutaneous blastomycosis was made. Potassium iodide was administered in gradually increasing amounts until the patient was receiving 4 cc. (80 drops) three times a day. Also, 400 roentgen units were administered to the cutaneous lesions over a period of a month. During the ensuing 4.5 years exacerbations caused hospitalization on three occasions and two additional courses of roentgen therapy were administered. The last radiation treatment consisted of 1,200 r given in the course of five weeks during March and April, 1948. A chest roentgenogram in 1946 disclosed calcifications in the right hilar area and high in the right peritracheal region. Minimal fibrosis and calcification were observed in the right upper lobe behind the second anterior interspace as well as in the left upper lobe posterior to the first and second interspaces. No miliary lesions were present. A subsequent chest film in 1947 revealed no alteration. (Fig. 1A.) In March, 1948, chest x-ray disclosed no change in the fibrocalcific areas but there was a very fine granular appearance to the lung fields which suggested very early miliary tuberculosis.

In the latter part of September, 1949, the facial lesions became quite painful and exuded

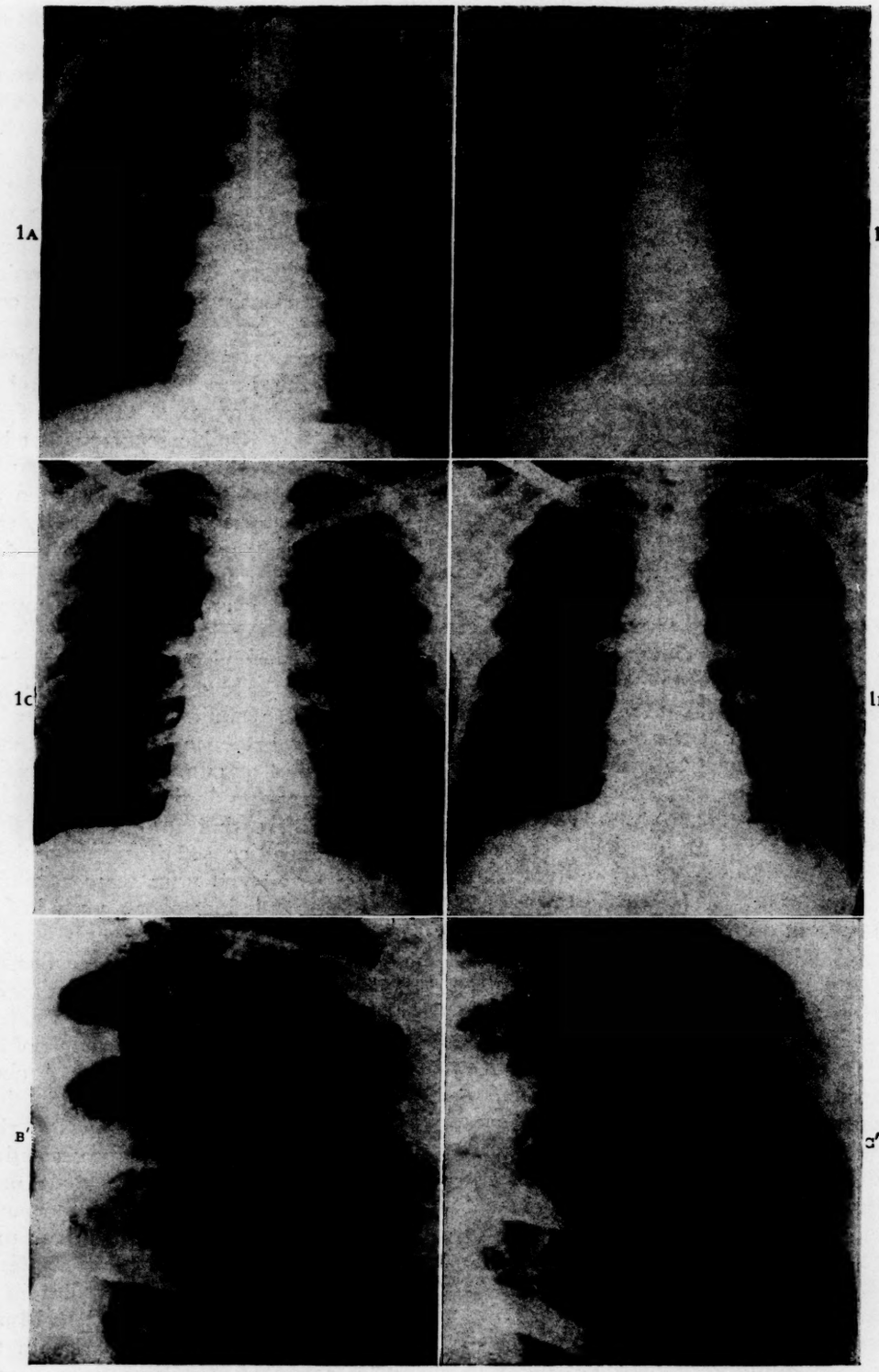


FIG. 1. A, Chest film in 1947 showing no miliary infiltration. B, routine admission film revealing diffuse miliary involvement; B′, (enlargement) left hilar area in admission film. C, after seven weeks of aureomycin therapy; definite clearing of lung fields is present; C′, (enlargement) left hilar area after seven weeks of aureomycin therapy. D, after four months of aureomycin; no miliary lesions are noted

a very foul-smelling, purulent material. The cervical lymph nodes were enlarged and tender. Shortly thereafter a chronic cough developed which was productive of a small amount of mucopurulent material. Associated with this cough was vague generalized chest pain and mild dyspnea on exertion. Low grade fever, malaise, progressive weakness and drenching night sweats had been noted for a month prior to hospitalization.

Examination upon admission to the hospital revealed that the temperature was 38.2°C., pulse 102, respirations 24 and blood pressure 130/86 mm. Hg. The patient was a well developed and well nourished Negro who did not appear acutely ill. There was extreme disfigurement of the face. (Fig. 5A.) The nose, forehead, cheeks and chin were included in cutaneous lesions characterized by a central pinkish, paper thin, atrophic area which was enclosed by a peripheral, elevated serpiginous zone. The centrifugal edge was elevated about 1 cm. above the skin surface and contained innumerable small abscesses. The entire face was secondarily infected and exuded such a foul odor that it was necessary to employ special deodorizing equipment about the patient. The nose had almost disappeared. Examination of the eyes was quite difficult because of extreme eversion of the upper eyelids as a result of marked scarification. Although the eye involvement had been present for six years, both corneas were normal. This was likewise true of both anterior chambers and irides. The cervical and axillary lymph nodes were greatly enlarged, woody in consistency and tender. Pulmonic examination disclosed moderate pain on deep inspiration and generalized fine rhonchi on auscultation. Aside from a sinus tachycardia cardiac examination was within normal limits.

Immediately upon admission to the Medical Service a biopsy of the serpiginous edge of the facial lesion was obtained. Also, purulent material from one of the small abscesses was examined microscopically and was cultured on Sabouraud's medium at room temperature and on blood agar at 37°C. All preparations revealed B. dermatitidis. Large numbers of these organisms were present in the biopsy tissue. (Fig. 2.) An admission chest roentgenogram revealed a miliary type of pulmonic involvement. (Fig. 1B.) No change has been noted at any time in the previously described fibro-calcific areas in both lung fields. Subsequently, B. dermatitidis was

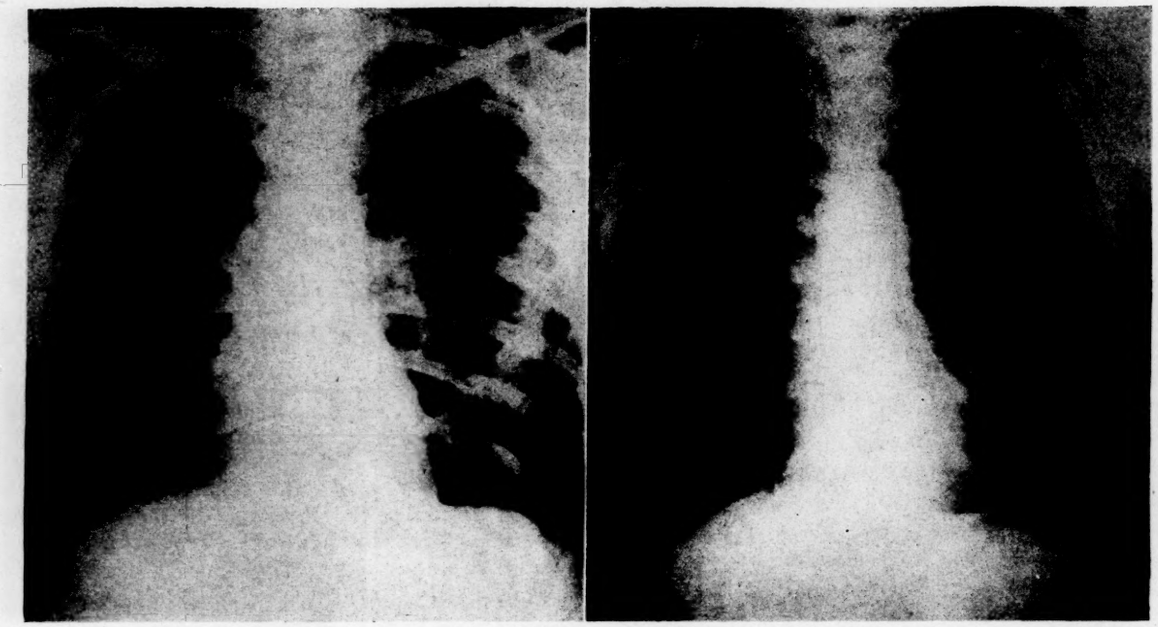
FIG. 2. Microscopic section of biopsied tissue from facial lesions showing B. dermatitidis in a giant cell.

demonstrated in three sputum specimens, in three bronchial washing specimens and in three gastric washing specimens. This established the diagnosis of systemic North American blastomycosis.

On December 6, 1949, aureomycin therapy was begun using 750 mg. orally every six hours. Continuous warm boric acid packs and ophthalmic aureomycin ointment were applied to the eyes and face. Weekly chest roentgenograms were obtained. A regular diet without supplementary vitamins was administered.

Two weeks after admission the cervical glands drained spontaneously; complete healing, however, occurred within six weeks. There was no definite evidence of pulmonic improvement until seven weeks after the institution of therapy (January 24, 1950). At that time there was evident clearing of the lung fields. (Fig. 1C.) Thereafter, progressive reduction was observed in the infiltrative lesions in both lung fields; four months after treatment had been instituted (March 13, 1950) the chest roentgenogram was regarded as within normal limits. (Fig. 1D.)

For the ensuing six months the same therapy was continued; that is, 3 gm. of aureomycin were administered daily. During this period the patient was afebrile, had a good appetite and maintained his weight. Twenty sputum specimens, twenty gastric washing specimens, six bronchial washing specimens and three urine specimens were negative for tubercle bacilli and B. dermatitidis. Therefore, ten months after treatment had been instituted, aureomycin was discontinued. At that time the patient had re-



3A 3B

FIG. 3. A, Chest film one month after aureomycin was discontinued; bilateral pulmonic involvement is obvious. B, four months after resumption of aureomycin; no miliary infiltration is apparent.

ceived 928 gm. of this antibiotic without significant toxic effects.

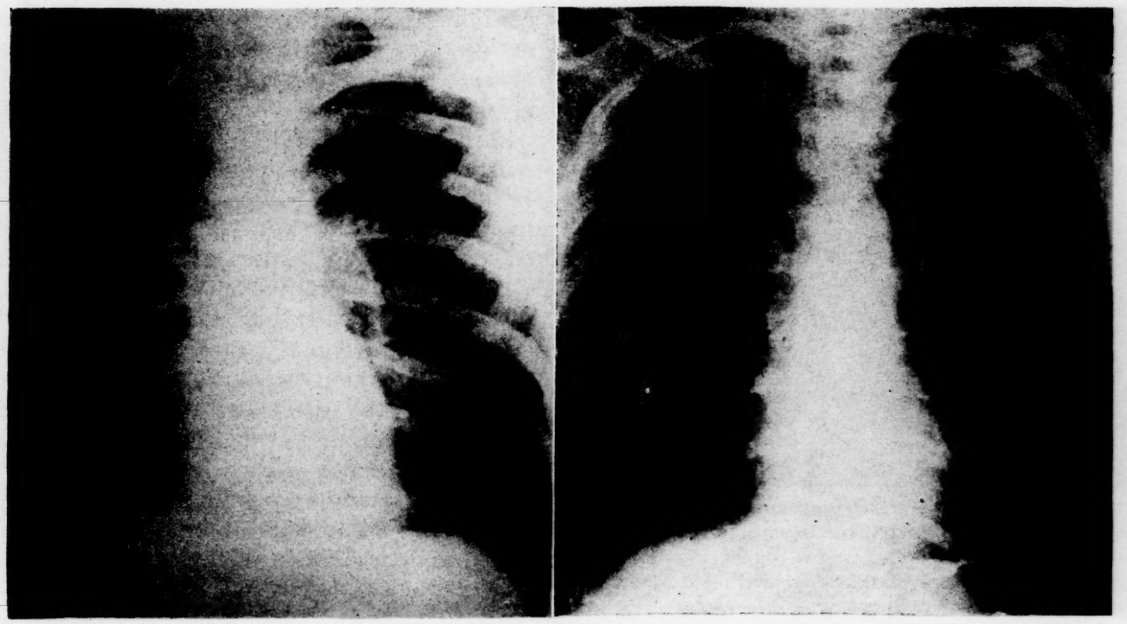
One month after aureomycin was discontinued the chest roentgenogram revealed a diffuse, granular, miliary process involving the entirety of both lung fields. (Fig. 3A.) Also, a low grade fever was present, especially in the morning, and night sweats had again become prominent. However, the appetite was good and there was no weight loss or feeling of weakness. A slight non-productive and non-painful cough was present. Two sputum and three gastric washing specimens again revealed B. dermatitidis but were negative for tubercle bacilli. Aureomycin was reinstituted using 4 gm. daily in divided doses. Four months later the lung fields were essentially clear (Fig. 3B) and repeated sputum and gastric washing examinations failed to reveal B. dermatitidis. The patient was asymptomatic and so aureomycin was again discontinued.

One month later the lung fields revealed diffuse granular involvement. (Fig. 4A.) On this occasion there was rapid weight loss (3.7 kg. in three weeks) and constant low grade fever was present.

Therefore, on April 25, 1951, aureomycin was once more begun using 4 gm. orally each day in divided doses. Three weeks later (May 15, 1951) there was definite diminution in the size of the infiltrative lesions and in two months (June 28, 1951) there was no evidence of the miliary lesions. (Fig. 4B.) Since reinstitution of therapy nine gastric washing specimens and three sputum specimens have failed to reveal B. dermatitidis. In 3.5 months the patient has gained 4 kg., is afebrile and is entirely asymptomatic. Repeated recent chest films have disclosed no evidence of fungal infection.

Gradual but definite improvement of the patient's facial lesions was observed during nineteen months of aureomycin treatment. All secondary infection disappeared shortly after hospitalization. However, B. dermatitidis could still be demonstrated in small numbers in biopsied tissue. Itching and burning of the face, which had been severe during the first months of treatment, were gradually reduced until in May, 1951, the patient stated that his face was better than at any time in the past 3.5 years. (Fig. 5B.)

In an effort to improve the facial lesions potassium iodide was begun as an adjunct to aureomycin. Initially 0.05 cc. (1 drop) of a saturated solution was administered orally three times a day; gradually this was increased until in ten days, the patient was receiving 4.5 cc. (90 drops) daily. The chest films remained clear and itching and burning of the face essentially disappeared. However, marked



4A 4B

FIG. 4. A, Chest film one month after aureomycin was discontinued a second time; there is diffuse granular involvement. B, two months after second resumption of aureomycin; there is no evidence of miliary lesions.

5A 5B

FIG. 5. A, Facial lesions before aureomycin. B, face after nineteen months of aureomycin, showing essential obliteration of elevated peripheral edge and new skin formation.

FIG. 6. A, B, and C are ten-day cultures of B. dermatitidis isolated from this patient. A contains no aureomycin, B contains 5,000 μg. and C 10,000 μg. per cc. of culture medium. Only minimal growth is evident in B and no growth is present in C.

swelling of the cervical lymph nodes and burning of the facial lesions became prominent on the second day during which the patient received 4.5 cc. (90 drops) of potassium iodide. Therefore, the iodide was progressively reduced and was finally discontinued after twenty days of use. At that time the patient was entirely asymptomatic and the facial lesions were markedly improved. After a rest period of ten days potassium iodide was again administered exactly as before. At the conclusion of this course of iodide therapy the facial lesions had virtually disappeared.

Therefore, the patient was discharged after twenty-one months of hospitalization to be followed up through the clinic. The patient is being maintained on 3 gm. of aureomycin daily; he is entirely asymptomatic and is gaining weight. The Ophthalmology Service has recommended a plastic repair of the eyelids and this operation will be performed within a few weeks.

Since this patient was receiving such prolonged and massive aureomycin therapy, the possibility of toxic reactions was anticipated. Initially, and every three months thereafter, a liver punch biopsy was performed and the material was examined microscopically; likewise, at the same periods, a sternal marrow aspiration was performed and was examined microscopically and by culture. A complete peripheral blood study and urinalysis were carried out each week, a blood non-protein nitrogen was obtained each month, an electrocardiogram every two months and four determinations of the urinary 17-ketosteroids were obtained during treatment in the hospital. All of these special procedures were consistently within normal limits.

Although this patient received a total of 1,908 gm. of oral aureomycin in twenty-one months, the only toxic effects noted were five transient bouts of nausea and vomiting. These were relieved within twelve hours by the administration of 100 mg. of pyridoxine hydrochloride intravenously each day for ten days. At no time was it necessary to interrupt treatment. For the first four months no supplementary vitamins were administered, yet there was no evidence of avitaminosis. After this period a vitamin cocktail was administered three times a day to promote convalescence.

Laboratory data in this case were as follows: Blood count: red cells ranged from 3,200,000 to 5,400,000; hemoglobin from 9.5 to 13 gm.; hematocrit from 33 to 45 per cent; white cells from 18,750 to 5,250; repeated differential white counts (sixty-eight) were normal. Urinalysis: weekly urinalyses were within normal limits. The sedimentation rate (Wintrobe, corrected) ranged from 1.2 to 0.3 mm. maximal fall per minute (Rourke-Ernstene technic); the blood non-protein nitrogen from 54 to 29 mg. per cent; total protein from 5.5 to 7.4 gm. per cent with the albumin from 3.3 to 4.2 gm. per cent and the globulin from 2.2 to 3.4 gm. per cent; prothrombin concentration from 71 to 100 per cent; total serum bilirubin from 0.3 to 0.9 mg. per cent; twenty-four-hour urine urobilinogen from 2.5 to 3.2 Ehrlich units; repeated determinations of retention of bromsulfalein (after forty-five minutes using 5 mg./kg. of body weight intravenously) were 5 per cent; repeated cephalin-cholesterol flocculation tests were negative; plasma cholesterol from 130 to 80 mg. per cent; fasting blood sugar from 75 to 118 mg. per cent. Two glucose tolerance tests were within normal limits. The blood Kahn test was negative. The intradermal tuberculin test (P.P.D.-first strength) was 1 + at forty-eight hours. Four determinations of the urinary 17-ketosteroids varied from 10 to 14 mg. in twenty-four hours. Thirty-two sputum specimens, twenty-nine gastric washing specimens and four sternal marrow specimens were negative for tubercle bacilli by microscopic examination and by culture.

Aureomycin blood levels ranged from 0.5 to

8 μg. per cc while the patient was under therapy in the hospital.

After receiving 1,908 gm. of oral aureomycin, gram-stained smears of two stool specimens were examined microscopically. With twenty fields counted and the results averaged, the number of bacteria per oil immersion field was as follows: gram-positive diplococci 39.0, gram-negative bacilli 15.5, gram-positive bacilli 2.0 and yeast 1.5.

Therefore, a preponderance of gram-positive organisms was observed. Stool cultures using routine aerobic and anaerobic procedures disclosed the following bacteria: Escherichia coli, E. coli mutabilis, Aerobacter aerogenes, Streptococcus faecalis, Str. viridans, Clostridium perfringens and Str. anaerobius. Cl. perfringens were present in such small numbers that they failed to appear on the original culture plates and were isolated from twenty-four-hour broth cultures.

In vitro sensitivity results: Using B. dermatitidis organisms isolated from this patient, a definite inhibitory action by aureomycin was demonstrated. (Fig. 6.) These studies were subsequently repeated with similar results. The control cultures (containing no aureomycin) revealed B. dermatitidis in five days; however, those cultures containing 20,000 μg. of aureomycin per cc. of medium were not positive for fourteen to thirty-eight days. With 40,000 μg. of aureomycin per cc. of medium no growth was evident at fifty-six days. (Table I.)

TABLE I
IN VITRO SENSITIVITY STUDIES ON B. DERMATITIDIS

	Strain of B. dermatitidis	μg. of Aureomycin per cc. of Medium				
		0.0	5,000	10,000	20,000	40,000
Series I	1 (Case I)	+ at 5 days	+ at 5 days	+ at 26 days	+ at 38 days	− at 56 days
	2 (Case II)	+ at 5 days	+ at 5 days	− at 30 days*	+ at 38 days	+ at 44 days
	3†	+ at 5 days	+ at 5 days	+ at 12 days	− at 26 days*	− at 56 days
	4†	+ at 5 days	+ at 5 days	+ at 5 days	+ at 12 days	+ at 30 days
	5†	+ at 5 days	+ at 5 days	+ at 12 days	+ at 56 days	− at 56 days
Series II	1 (Case I)	+ at 5 days	+ at 14 days	+ at 14 days	+ at 14 days	.....‡
	2 (Case II)	+ at 5 days	+ at 14 days	− at 28 days	− at 28 days	.....
	3†	+ at 5 days	+ at 14 days	− at 28 days	− at 28 days	.....
	4†	+ at 5 days	+ at 5 days	+ at 14 days	− at 28 days	.....
	5†	+ at 5 days	+ at 5 days	− at 28 days	− at 28 days	.....

+ Indicates growth; − indicates no growth.
* The medium was contaminated but no growth of B. dermatitidis was present.
† These strains were supplied by Dr. N. G. Conant of Duke University.
‡ This concentration of aureomycin was not employed in series II.

CASE II. A thirty-three year old white male laborer from Arkansas was admitted to the Medical Service of the John Gaston Hospital on April 18, 1950, with the diagnosis of systemic North American blastomycosis.

In September, 1949, this patient was observed in the outpatient department of a Memphis hospital. At that time he complained of multiple, chronic, cutaneous lesions on the face, neck and upper extremities. This patient stated that his illness dated from 1944 when he scratched a pimple on his neck. Two months later this lesion had expanded to a diameter of about 4 cm. For a year only a single ulcer was noted; then additional similar lesions developed. A diagnosis of cutaneous blastomycosis was made by a private physician and the patient responded well to increasing amounts of potassium iodide. He remained on a regimen of 12 cc. (240 drops) daily of this medication for fourteen months. Upon moving to another locality he discontinued medication and an exacerbation followed in approximately one year. Again improvement was noted after the resumption of potassium iodide in the same dosage as before. This recession of the disease persisted for twenty months. From 1944 to

1948 three chest films were said to have shown no abnormal findings.

In September, 1949, this patient was observed in the medical outpatient department of a Memphis hospital. At that time multiple cutaneous lesions were noted on the face, neck and upper extremities. The diagnosis of blastomycosis was verified by microscopic and cultural examinations. Chest roentgenogram revealed a fibrotic area in the right upper lobe, and a diagnosis of systemic North American blastomycosis was made after the specific organisms were demonstrated in the sputum and in the urine. Potassium iodide was administered orally in gradually increasing amounts until in three weeks the patient was receiving 4.5 cc. (90 drops) three times a day. During the ensuing three months this medication was continued, with no alteration of the clinical picture. Therefore, on January 8, 1950, he was referred to the General Medicine Clinic of the John Gaston Hospital and the University of Tennessee College of Medicine with the diagnosis of systemic North American blastomycosis.

When first observed in our clinic the patient complained of severe, constant itching and burning of the cutaneous lesions. Although no malaise or weakness had been noted, there had been a weight loss of 2.8 kg. in the previous month and a low grade fever had been present during this period. A non-productive and non-irritating cough had been noted for ten years; slight hemoptysis had been observed for two years.

Examination in the clinic revealed that the temperature was 38.6°c., pulse 108, respirations 28 and blood pressure 118/75 mm. Hg. The patient was a well developed and well nourished white male who had seven cutaneous lesions on the face, neck and upper extremities. These varied in size from a diameter of 4 to 11.5 cm. These lesions had a central, pinkish, atrophic area which appeared to be healing and an elevated, serpiginous, peripheral border containing multiple small abscesses. The involved areas were only moderately painful. A painless subcutaneous nodule measuring 1.5 cm. in diameter, which had been present for two months, was located on the flexor surface of the left forearm; a similar lesion 2 cm. in diameter was noted just to the left of the umbilicus. This lesion had been present three to five weeks and was believed to be increasing in size. The patient stated that the last lesion to appear on his neck had developed in such a manner and had finally ulcerated. Pulmonic examinations disclosed fine crackling rales in the right upper lobe. Aside from a sinus tachycardia, cardiac examination was within normal limits.

B. dermatitidis organisms were demonstrated in biopsied tissue from the lesions and in purulent material from the cutaneous ulcers as well as in cultures of the sputum, bronchial washings and gastric washings. The patient was instructed to apply boric acid dressings to the lesions each day and was given 750 mg. of aureomycin orally four times a day. At this time he declined hospitalization.

On April 18, 1950, (four months after therapy was begun) the patient was admitted to the Medical Service of the John Gaston Hospital because of severe secondary infection of the cutaneous lesions. Oral aureomycin was continued for the ensuing seven months using 4 gm. daily in divided doses. Although this patient received 1,042 gm. of oral aureomycin in eleven months, no toxic reactions were observed. Not even nausea was noted. During treatment four liver biopsies and four sternal marrow aspirations revealed no evidence of toxic effects to this antibiotic; likewise, two determinations of the urinary 17-ketosteroids, three basal metabolic rate determinations and numerous other studies failed to disclose any derangement of metabolism. While hospitalized the patient gained 8 kg. in weight and remained afebrile. Fourteen sputum specimens, six bronchial washing specimens and fifteen gastric washing specimens were negative for B. dermatitidis, other fungi and tubercle bacilli.

However, although the cutaneous involvement did improve and serial biopsies revealed an apparent reduction in the number of organisms, the lesions remained; and B. dermatitidis could be demonstrated in the biopsied tissue. Therefore, after eleven months of treatment it was decided to administer potassium iodide in conjunction with aureomycin. The amount of iodide was increased gradually to 3.75 cc. (75 drops) three times a day. There was rapid clinical response and in three weeks the patient was discharged to be followed up through the clinic. During this patient's illness sixteen chest roentgenograms were obtained; no alteration was observed; in all there appeared to be an area of chronic fibrosis in the right upper lobe.

Three months after discharge from the hospital the patient moved to another locality

and further observation was impossible. When last examined there was no evidence of the systemic form of this infection. At that time the patient was being maintained on potassium iodide and on 3 gm. of aureomycin daily.

Laboratory findings in this case were as follows: Blood count: red cells ranged from 3,900,000 to 5,240,000; hemoglobin from 12 to 14.5 gm.; hematocrit from 38 to 46 per cent; white cells from 11,050 to 6,900; multiple differential leukocyte counts were within normal limits. Weekly urinalyses were within normal limits. The sedimentation rate (Wintrobe, corrected) ranged from 0.86 to 0.2 mm. maximal fall per minute (Rourke-Ernstene technic); the blood non-protein nitrogen from 26 to 32 mg. per cent; total protein from 6.0 to 7.1 gm. per cent with the albumin from 4.2 to 4.8 gm. per cent and the globulin from 1.8 to 2.3 gm. per cent; total serum bilirubin from 0.7 to 0.9 mg. per cent with a one-minute value from 0.1 to 0.2; multiple determinations of bromsulfalein retention in blood (45 minutes using 5 mg. per kg. of body weight intravenously) from 2 to 0 per cent retention; cephalin-cholesterol flocculation tests were persistently negative; plasma cholesterol from 134 to 155 mg. per cent; fasting blood sugar from 83 to 108 mg. per cent; two glucose tolerance tests were within normal limits. The blood Kahn test was negative. Basal metabolic rate determinations ranged from −8 to +4 per cent; urinary 17-ketosteroids from 8 to 18 mg. in twenty-four hours. The intradermal tuberculin (P.P.D.-first strength) was ++ at forty-eight hours. Multiple cultures of the sputum, bronchial washings and gastric washings were negative for tubercle bacilli. Aureomycin blood levels ranged from 1 to 8 μg. per cc.

In vitro sensitivity results: Using B. dermatitidis organisms isolated from this patient a definite inhibitory action by aureomycin was demonstrated. Although control cultures (not containing aureomycin) disclosed growth of the fungus in five days, it required at least thirty-eight days in those containing 20,000 μg. of aureomycin per cc. of medium. (Table I.)

COMMENTS

Many physicians regard blastomycosis as a rare and most unusual disease. However, sixteen cases have been observed at the John Gaston Hospital and the University of Tennessee College of Medicine in the past ten years. Of these, eleven were of the systemic variety and five were of the cutaneous type.

It is quite probable that many cases of this disease are misdiagnosed as tuberculosis. Clinically, these conditions may be quite similar, and even gross examination at necropsy may yield a false diagnosis. Frequently, microscopic and bacteriologic examinations are necessary at postmortem to rule out tuberculosis. In all chronic pulmonic cases simulating tuberculosis in which tubercle bacilli cannot be readily demonstrated blastomycosis should be considered. Occasionally, as in one patient observed at the John Gaston Hospital, the two diseases occur together. Bronchogenic carcinoma is also probably confused with blastomycosis. With improved and more readily available laboratory facilities, blastomycosis should be recognized with increasing frequency.

In the two cases reported here, an encouraging clinical response to aureomycin was obtained. In one patient (Case I) with proven systemic blastomycosis pulmonic involvement disappeared roentgenologically after four months of intensive aureomycin therapy. During the ensuing six months, while the patient remained on 3 gm. of aureomycin daily, nineteen chest films were interpreted as being within normal limits. There were no toxic or debilitating signs of the systemic form of this disease. Multiple examinations of the sputum, bronchial washings and gastric washings revealed no fungi. However, one month after aureomycin was discontinued bilateral pulmonic involvement recurred and fungi could be readily demonstrated. The prompt reinstitution of aureomycin therapy caused rapid clearing of the lung fields although discontinuance of this antibiotic once more resulted in marked pulmonic involvement. Rapid pulmonic and systemic improvement followed the third course of therapy. This case indicates that B. dermatitidis organisms develop little resistance to aureomycin. As long as the patient received no more than 4 gm. of aureomycin a day no significant toxic effects were noted (only five transient periods of nausea and vomiting). Exceeding this amount of medication, however, resulted in persistent gastric distress. *In vitro* sensitivity studies using B. dermatitidis organisms isolated from this patient established a definite inhibitory action by aureomycin. (Fig. 6.)

In the second patient (Case II) gastric specimens, sputum specimens and bronchial washings became negative for B. dermatitidis on

aureomycin therapy. Two subcutaneous nodules disappeared. Sensitivity studies demonstrated an inhibitory effect by aureomycin. (Table 1.) No satisfactory follow-up was possible in this case.

Because these two patients received massive amounts of aureomycin over a prolonged period of time, comprehensive studies were performed to detect any evidence of toxic effects to this antibiotic but none were observed.

Through the courtesy of Dr. N. G. Conant of Duke University, three additional strains of B. dermatitidis were obtained for study. *In vitro* sensitivity investigations using these organisms were carried out with aureomycin. There was definite evidence of inhibition. (Table 1.)

As a result of the clinical and laboratory studies reported in this article, it would appear that aureomycin is capable of prolonged control of systemic North American blastomycosis. Whether it will be possible to obtain sufficiently high levels *in vivo* to eradicate the fungi is not yet clear. Perhaps the simultaneous use of some preparation to reduce the excretory rate of this antibiotic may produce the desired tissue and vascular concentrations or perhaps the combination of aureomycin and other agents may result in a synergistic action leading to the destruction of B. dermatitidis in the body.

Aureomycin appears to be a promising agent for the treatment of systemic North American blastomycosis and would seem to deserve further trial.

SUMMARY

1. The literature concerning systemic North American blastomycosis was reviewed.

2. Two patients with proven systemic North American blastomycosis were treated by the prolonged administration of oral aureomycin with encouraging results.

3. Extensive clinical and laboratory studies indicated that the toxicity of aureomycin administered over this prolonged period was minimal.

4. *In vitro* sensitivity studies established an inhibitory effect by aureomycin on five strains of B. dermatitidis.

5. Aureomycin appears to be of value in the treatment of systemic North American blastomycosis and further trial would seem to be indicated.

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Tuberculous Pericarditis*

Its Treatment with Streptomycin and Some Observations on the Natural History of the Disease

THEODORE M. MYERS, M.D. *and* MORTON HAMBURGER, M.D.
Cincinnati, Ohio

TUBERCULOUS pericarditis, although not in itself a primary infection, is occasionally the most important clinical manifestation of tuberculosis. Experience has shown[1,2] that the ultimate prognosis is usually poor either because the patient dies of circulatory failure or because the pericarditis proves to be the harbinger of widespread dissemination of tubercle bacilli within a few months. Very infrequently the pericarditis heals and the patient enjoys good health for a year or more[1] but even in these instances active tuberculosis nearly always appears later in some other part of the body. Various names have been suggested to designate this kind of pericarditis, such as clinically primary tuberculous pericarditis, but none are entirely satisfactory.

During the past three years we have had the opportunity to treat with streptomycin three patients who had tuberculous pericarditis with effusion in whom the pericardial involvement was clinically the most important feature of the patient's disease. None of these patients suffered from demonstrable pulmonary tuberculosis although pleural effusion was present in two cases. The success of the treatment and the well-being of the patients during the twenty-four- to thirty-one-month follow-up periods has prompted us to report our experience. It is the purpose of this article to present these patients along with a study of nine similar patients treated at the Cincinnati General Hospital but not given chemotherapy. Most of these nine patients were not seen by the authors.

Natural History of Tuberculous Pericarditis in Nine Patients Who Did Not Receive Chemotherapy. These cases were divided into two rather distinct groups. In the first were five patients who died shortly after admission either of cardiac failure or of extensive pulmonary or miliary disease resulting from early dissemination. In the second group were four patients who showed definite evidence of pericardial healing and who for relatively long periods were completely asymptomatic only to return later with tuberculosis in some other part of the body.

The five patients in the first group all presented the clinical picture of tuberculosis of the pericardium when originally seen. Although pleurisy was present on admission in three cases and peribronchial infiltration in one, they played a secondary role to the pericarditis. Dissemination of the tuberculosis occurred under observation in three patients within nine and one-half weeks to eleven months. Two patients died of miliary tuberculosis twenty-four and twenty-six days after admission. One might strongly consider the possibility that they had miliary disease when they were first seen even though the only demonstrable clinical manifestation was the pericarditis. Table 1 presents the findings upon which the diagnosis of tuberculous pericarditis in these patients was based.

The course of the disease in the second group differed from that of the first in three important respects: (1) there was an extended period during which these patients were asymptomatic; (2) when reactivation of tuberculosis occurred, it did not involve the pericardium which apparently had healed; and (3) although three of the four patients ultimately died, the survival time following spontaneous recovery from pericarditis was considerably prolonged. Two succumbed to miliary tuberculosis and the third died of extensive pulmonary involvement. In the fourth patient, who is still living, tuberculous peritonitis developed less than twelve months after recovery from the pericarditis. She was

* From The Department of Medicine, University of Cincinnati College of Medicine and the Cincinnati General Hospital, Cincinnati, O.

treated with streptomycin and since has been perfectly well. The important diagnostic findings in this group are summarized in Table II.

Although all the patients in groups I and II had what has been called clinically primary tuberculosis of the pericardium, it is clear that that the patients with recurrent tuberculosis elsewhere in the body no longer have active pericarditis. It is possible, then, that tracheobronchial and mediastinal lymph nodes, rather than the pericardium, represent the focus for reinfection.

TABLE I

GROUP I—UNTREATED PATIENTS WITH PERICARDIAL EFFUSION FOLLOWED WITH PROGRESSIVE TUBERCULOSIS—DIAGNOSTIC CRITERIA

	Evidence of Pericarditis		Evidence of Pericardial Effusion			Evidence of Tuberculosis	
Patient	Friction Rub	EKG	Physical Examination	X-ray	Pericardial Tap	AFB† in Pericardial Fluid	Postmortem Findings
O. C.	+	+	+	+	+	+	*
J. B.	+	+	+	+	+	+	*
W. H.	-	+	+	+	+	+	*
F. W.	-	+	+	+	+	+	*
W. M.	+	+	+	+	*	*	+

\+ = Present
\- = Absent
* = Not done
†AFB = Acid-fast bacilli

TABLE II

GROUP II—UNTREATED PATIENTS WITH PERICARDIAL EFFUSION WHO SHOWED SPONTANEOUS HEALING—DIAGNOSTIC CRITERIA

	Evidence of Pericarditis		Evidence of Effusion			Evidence of Tuberculosis		
Patient	Friction Rub	EKG	Physical Examination	X-ray	Pericardial Tap	AFB† in Pericardial Fluid	Postmortem Findings	Other
W. H.	+	+	+	+	*	*	+	
M. W.	+	+	+	+	*	*	+	
M. L.	-	+	+	+	+	*		Tuberculosis peritonitis 1 year later proved at operation
L. H.	+	+	+	+	+	*		Tubercle bacilli in pleural fluid

\+ = Present
\- = Absent
* = Not done
†B = Acid-fast bacilli

they have followed widely divergent courses. Such a patient may die shortly after admission to a hospital either of congestive failure or of miliary spread which probably takes place at the time of the pericardial involvement. He may have a more protracted course, terminating finally in extensive pulmonary or miliary tuberculosis. He may show spontaneous healing of the pericarditis only to return months or years later with tuberculosis in some other part of the body. There is clinical and pathologic evidence

Treatment of Tuberculous Pericarditis with Streptomycin. Until the advent of streptomycin, repeated pericardiocentesis, sometimes accompanied with injection of air, was the most popular treatment of the acute stage of the infection although pericardiotomy and partial pericardiectomy had also been used. In 1947 McDermott et al.[3] reported, among a group of patients with various forms of disseminated tuberculosis treated with streptomycin, three patients with associated pericarditis. One of

them had lymphadenitis; the other two had miliary pulmonary lesions. The former patient was perfectly well eleven months after the completion of therapy; the latter two patients showed marked diminution in the size of the cardiac silhouette and clearing of the pulmonary lesions but there is no statement as to their subsequent course. In 1949 Meredith[4] reported a case of presumably tuberculous pericarditis and tuberculous axillary lymphadenitis treated with streptomycin for thirty-three days. Although there was a gradual decrease in cardiac size, this patient developed a pulmonary lesion and was transferred to another hospital. In 1949 Johnson and Bercu[5] reported three patients who showed striking improvement under streptomycin therapy but no statement was made regarding the subsequent period of observation.

TABLE III

GROUP III—PATIENTS WITH TUBERCULOUS PERICARDIAL EFFUSION TREATED WITH STREPTOMYCIN—DIAGNOSTIC CRITERIA

	Evidence of Pericarditis		Evidence of Effusion			Evidence of Tuberculosis
Patient	Friction Rub	EKG	Physical Examination	X-ray	Pericardial Tap	AFB† in Pericardial Fluid
E. C.	+	?	+	+	+	+
W. G.	+	+	+	+	+	+
J. C.	+	+	+	+	+	+

\+ = Present
\- = Absent
* = Not done
†AFB = Acid-fast bacilli

We have observed the effect of streptomycin therapy in three patients with proved tuberculous pericarditis with effusion. No other active tuberculosis could be demonstrated elsewhere in the body in two cases when they were first seen; one patient had a pleural effusion in addition to pericarditis. Two patients received 1 gm. of streptomycin intramuscularly daily for ninety days; the third 1 gm. daily for 112 days. In addition, each had at least one pericardiocentesis. The important diagnostic findings are presented in Table III.

Had streptomycin not been given to these patients it is possible that the pericarditis might have healed spontaneously, as was the case in our group I patients. On the other hand they might have died of circulatory failure or dissemination of the tuberculosis as in the group II cases. Compared with the latter group, the three treated patients have done very well indeed. However, a comparison with the average course of the four patients whose pericarditis healed without the help of chemotherapy provides a more rigid test for streptomycin. Two criteria have been chosen as a basis for this comparison: the duration of fever while the patient was in the hospital and, more important, the duration of the asymptomatic period following the fall of temperature to normal.

The duration of fever is shown in Table IV. In both the treated and untreated groups the average febrile period is measured from the time the patient was admitted to the hospital until the temperature became normal. The average of less than thirteen weeks in the treated group compares favorably with the average of more than twenty-one weeks in the untreated group. Furthermore, since in the treated group streptomycin was withheld for two weeks or longer pending diagnostic studies, the febrile period after the institution of chemotherapy was shorter than the thirteen-week average shown in the table.

Defervescence following institution of streptomycin therapy was not dramatic. Clinical improvement, including diminution in size of the cardiac silhouette, similarly was gradual. In all three cases complete absorption of the fluid, with return of the venous pressure to normal, had occurred by the time the patient left the hospital.

Of greater significance in evaluation of the role of streptomycin in this series is the condition of the treated patients at the time of the present report as compared with the asymptomatic period in the group in which spontaneous healing took place but with subsequent recrudescence of tuberculosis elsewhere in the body. In the latter group the average period of well-being

was 16.5 months and the longest twenty-four months. By comparison, the treated patients are all asymptomatic and leading normal lives at an average of twenty-eight months after the cessation of therapy, the longest being thirty-one months.

TABLE IV

DURATION OF FEVER IN HOSPITAL IN GROUPS II AND III AND ASYMPTOMATIC PERIOD AFTER SPONTANEOUS HEALING (GROUP II) COMPARED WITH DURATION OF FOLLOW-UP (GROUP III)

Group	Patient	Duration of Fever (wk.)	Asymptomatic Period after Spontaneous Healing (mos.)	Duration of Follow-up (mos.)
II (untreated)	W. H.	4	24	.....
	M. W.	25	> 7	.....
	M. L.	>26	< 12	.....
	L. H.	30	23	.....
	Average	>21	< 16.5	.....
III (treated with streptomycin)	E. C.	9	.....	31
	W. G.	< 19	.....	31
	J. C.	11	.....	24
	Average	< 13	.....	28

COMMENTS

In discussing the natural history and treatment of tuberculosis of the pericardium it is necessary to define as carefully as possible the terms used. Although clinically primary tuberculosis of the pericardium has been used to describe those cases in which there is no clinical evidence of the disease elsewhere, it is obvious from the material presented that tuberculosis often does exist in other parts of the body and that this situation has a significant bearing upon the prognosis.

Although instances have been reported in which the pericardial lesion seemed to be primary in a strictly anatomic sense, such cases are rare[6–10] in comparison with the incidence of the clinically primary type. Most writers believe that the latter occurs as a result of extension from adjacent tracheobronchial or mediastinal lymph nodes. William Osler expressed this view in 1893[11] and it has been more recently emphasized by Harvey and Whitehill.[1]

Although it is clear that spontaneous healing of the pericardial lesion sometimes takes place, the ultimate prognosis in this group of patients is certainly not favorable. Thus of thirty-seven acceptable cases of clinically primary tuberculous pericarditis found in the literature by Stepman and Owyang[12] 63 per cent died within six months and at least 84 per cent ultimately had fatal outcomes. In our group of nine untreated patients the mortality rate within six months was 44 per cent and the over-all mortality 89 per cent (one patient who received streptomycin for peritonitis is still living).

One of the interesting points about our untreated patients is that four of them had relatively long periods during which they were presumably afebrile and asymptomatic. The clinical and pathologic evidence suggests that the pericarditis had healed. We, therefore, believe that the subsequent appearance of tuberculosis in other tissues represented dissemination from the original tuberculous focus wherever it may have been. The possibility of reinfection seems less likely.

The ultimate evaluation of streptomycin in the treatment of tuberculous pericarditis must await the accumulation of more data and of longer follow-up periods. The three patients reported in this article seemed to derive real benefit from the drug. However, the Veterans Administration experience, as reported by Falk and Ebert,[13] shows that streptomycin is by no means universally effective.

CASE REPORTS

Group I. In this group there were six patients with progressive disease.

CASE I. O. C., a twenty-three year old colored man, entered the hospital on October 21, 1944, complaining of chest pain and weight loss during the preceding three weeks. His temperature was 102°F., pulse 110 and blood pressure 96/66. He was found to have cardiac enlargement, a pericardial friction rub and fluid in the right pleural space.

The electrocardiogram showed inverted T waves. X-ray studies revealed enlargement of the cardiac shadow with diminished pulsations, pulmonary congestive changes and a right-sided pleural effusion. Pericardial and pleural fluid were aspirated and tubercle bacilli were demonstrated in both by guinea pig inoculation.

Two months later signs and symptoms of meningitis appeared. The cerebrospinal fluid contained 100 white blood cells per cubic millimeter, of which 78 per cent were lymphocytes; the protein was 157 mg. per cent and the sugar 45 mg. per cent. The smear was negative for acid-fast bacilli. His course was progressively downhill and he died, apparently of tuberculous meningitis, nine and one-half weeks after admission. No postmortem examination was obtained.

CASE II. J. B., a thirty-two year old colored man, was admitted to the hospital on February 15, 1940, because of fever, shortness of breath and epigastric pain of four weeks' duration. His temperature was 103°F., pulse 120 and blood pressure 120/80. He was found to have pulsus paradoxus, venous distention, cardiac enlargement with distant heart sounds, a pericardial friction rub, Ewart's sign and hepatomegaly.

The electrocardiogram showed ST segment depression and T wave inversion. X-ray studies revealed enlargement of the cardiac shadow with diminished amplitude of pulsations. Tubercle bacilli were demonstrated in the pericardial fluid by guinea pig inoculation. The sputum was negative for acid-fast bacilli. Eight weeks later bilateral supraclavicular nodes were noted and there was x-ray evidence of pulmonary involvement.

On August 23, 1940, he was transferred to the Hamilton County Tuberculosis Sanitorium. There, repeated pericardial taps were performed but the patient failed to improve because mild congestive heart failure and more extensive pulmonary disease developed. He died nine months after admission, apparently of central nervous system involvement. No postmortem examination was obtained.

CASE III. W. H., a thirty-seven year old colored man, entered the hospital on July 22, 1944, complaining of cough for the preceding eleven months. He had otherwise been well until ten days before admission when dyspnea, orthopnea and chest pain developed. His temperature was 102°F., pulse 120 and blood pressure 90/75. Pulsus paradoxus was present, the heart was enlarged to the right and left and the sounds were distinct. Rales were heard at both lung bases and a pleuritic friction rub was heard at the right base.

The sputum was negative for acid-fast bacilli. The pericardium was tapped and bloody fluid obtained. It contained 3,000 white blood cells per cubic millimeter, all lymphocytes. Tubercle bacilli were demonstrated by guinea pig inoculation. X-ray showed generalized increase in the cardiac silhouette, and after injection of air into the pericardial cavity a thickened pericardium was demonstrated. Although repeated pericardial taps were performed, fluid continued to reaccumulate and also appeared in both pleural cavities. Four months after admission x-rays showed nodular areas of peribronchial infiltrate in both lung fields.

At this time he was transferred to the Hamilton County Tuberculosis Sanitorium. His condition deteriorated, he became confused and finally died about eleven months after the onset of symptoms. A postmortem examination was not obtained.

CASE IV. F. W., a twenty year old colored man, entered the hospital on February 18, 1939, complaining of headache, cough and left chest pain during the preceding week. His temperature was 102°F., pulse 130 and blood pressure 95/60. On physical examination the heart was slightly enlarged, there was fluid in the left hemithorax and a pleuropericardial friction rub was heard.

The chest film showed marked generalized cardiac enlargement and a left pleural effusion. The electrocardiogram showed changes consistent with pericarditis. A pericardiocentesis was performed and 30 cc. of hemorrhagic fluid obtained. It contained 1,500 white blood cells per cubic millimeter, of which 50 per cent were lymphocytes. Tubercle bacilli were demonstrated by guinea pig inoculation.

Three days after admission the patient developed neck vein distention and for the first time was noted to have pulsus paradoxus. On his eighth hospital day his respirations were

noted to be accelerated and cyanosis was present. In spite of repeated thoracenteses and pericardiocenteses he rapidly failed and died twenty-four days after admission.

At postmortem examination he was found to have tuberculous pericarditis, the pericardial sac containing 900 cc. of blood-tinged fluid. He also had tuberculous pleuritis, hilar lymphadenitis, splenitis and active peribronchial pulmonary tuberculosis. There was chronic passive congestion of the lungs and abdominal viscera.

CASE V. W. M., a sixty-eight year old colored man, entered the hospital on December 24, 1933, complaining of cough, loss of appetite and weight loss during the preceding three weeks. His temperature was 101°F., pulse 100 and blood pressure 170/110. He was found to have venous distention, cardiac enlargement with distant heart sounds and coarse inspiratory and expiratory rales throughout both lung fields.

A chest film showed generalized cardiac enlargement and infiltrative changes along the bronchial markings suggesting pulmonary congestion. The electrocardiogram showed low voltage of the QRS complexes with T wave changes. Smears of the sputum were repeatedly negative for acid-fast bacilli.

Ten days after admission the signs of fluid in the left pleural cavity and a distinct pericardial friction rub developed. A thoracentesis was done and 600 cc. of straw-colored fluid removed. It contained 200 white blood cells per cubic millimeter, all lymphocytes. The patient ran a febrile course, gradually became weaker and died twenty-six days after admission.

The postmortem examination showed a greatly thickened opaque pericardium. The pericardial cavity contained 600 cc. of cloudy yellow fluid. Minute gray nodules were found throughout the lung parenchyma and in the hilar lymph nodes. There was chronic passive congestion of the lungs and abdominal viscera. The pertinent anatomic diagnoses were tuberculous pericarditis, miliary tuberculosis of the lungs with beginning tuberculous pleuritis, chronic passive congestion of the lungs and abdominal viscera, and arrested hilar node tuberculosis.

Group II. In this group there were four patients who showed spontaneous healing without chemotherapy.

CASE I. W. H., a sixty-one year old colored man, entered the hospital on July 22, 1940, complaining of cough and chest pain of two weeks' duration. His temperature was 99°F., pulse 112 and blood pressure 130/90. The heart borders were enlarged to percussion and a loud pericardial friction rub was heard. The electrocardiogram showed T wave inversion. The chest film revealed an enlarged globular heart. With bed rest alone the cardiac silhouette diminished in size and after six weeks of hospitalization the patient became afebrile and was discharged.

He was apparently well for the next twenty-four months, returning at that time with a pleural effusion. Although tubercle bacilli could not be demonstrated in the pleural fluid, he was hospitalized for nine months. Following discharge he was quite well but nine months later he returned because of sensory disturbances and weakness of the left arm and leg. The spinal fluid protein was elevated, but all other studies were negative. He became mentally confused and gradually failed, dying four months later.

Postmortem examination showed healed pulmonary tuberculosis and extensive pleural and pericardial adhesions. Active tuberculosis was present in the peritoneum and in the adrenal glands and a tuberculoma was found in the mid-brain. His death occurred almost exactly four years after the onset of his initial symptoms of pericarditis.

CASE II. M. W., a forty year old colored man, entered the hospital on July 8, 1943, complaining of feeling ill for three months, with shortness of breath for two weeks. His temperature was 102°F., pulse 130 and blood pressure 136/90. The heart sounds were distant and a pericardial friction rub was heard.

A chest x-ray showed calcification in both upper lung fields and enlarged hilar nodes. The heart was enlarged with a straight left border and the contour was suggestive of a pericardial effusion. Fluoroscopically, however, good pulsations were seen. The electrocardiogram showed T wave inversion. Sputa and gastric washings were examined repeatedly for tubercle bacilli but none could be found. After six months he became afebrile and six months later was discharged. At this time the cardiac silhouette was normal radiologically.

Three weeks later he returned to the hospital with fever, chills, headache and malaise. The significant physical findings were nuchal rigidity and positive Kernig and Brudzinski signs. The spinal fluid contained 200 white blood cells per cubic millimeter (156 lymphocytes); the protein was 187 mg. per cent and the sugar 30 mg. per

cent. The clinical diagnosis was tuberculous meningitis but there was no evidence of tuberculosis elsewhere in the body.

The patient died shortly and postmortem examination which was limited to the head confirmed the clinical impression. Seventeen months elapsed from the onset of his pericarditis until his death.

CASE III. M. L., a thirty-nine year old colored woman, was admitted to the hospital on October 1, 1946, because of cough and pleuritic left chest pain of three weeks' duration. She had also noted shortness of breath and swelling of the ankles for four days prior to entry. Her temperature was 99°F., pulse 100 and blood pressure 150/130. She had pulsus paradoxus, distended neck veins, cardiac enlargement, distant heart sounds and bilateral pleural effusions.

The electrocardiogram showed depressed ST segments and T wave inversion. X-ray studies revealed enlargement of the cardiac shadow with diminished pulsations and bilateral pleural fluid, but no parenchymal lesion was demonstrated. Pericardiocentesis was performed on the second hospital day and 250 cc. of bloody fluid containing 4,200 white blood cells per cubic millimeter (95 per cent lymphocytes) was removed with dramatic relief of symptoms, decrease in venous pressure and increase in pulse pressure. Organisms could not be demonstrated in this material by smear, culture or guinea pig inoculation. However, tubercle bacilli were cultured from the pleural fluid. She gradually improved, showing definite reduction in cardiac size. Although still febrile, she left the hospital against advice after seven months.

She was well for the next twelve months and then returned with tuberculous peritonitis. There was no evidence of pulmonary, pleural or pericardial tuberculosis. She was treated with streptomycin, became afebrile after five weeks and was discharged after three months. Twenty months elapsed between the onset of symptoms of pericarditis and the development of peritonitis. She has since been perfectly well.

CASE IV. L. H., a seventeen year old colored man, was admitted to the hospital on July 16, 1941, with a one-month history of cough, chest pain and night sweats. His temperature was 102°F., pulse 110 and blood pressure 108/76. He was found to have cardiac enlargement with distant heart sounds, a pericardial friction rub and a pleural effusion on the left side.

The electrocardiogram showed T wave inversion. The chest film revealed a globular heart and fluoroscopy demonstrated diminished cardiac pulsations. The pericardial fluid was bloody, contained 1,300 white blood cells per cubic millimeter (77 per cent lymphocytes) and revealed no organisms on smear. Culture and guinea pig inoculation were not carried out. The pleural fluid was straw colored, containing 1,600 white blood cells per cubic millimeter of which 69 per cent were lymphocytes; tubercle bacilli were demonstrated in an inoculated guinea pig. The sputum was repeatedly negative.

He gradually improved and became afebrile twenty-nine weeks after admission. There was x-ray evidence of gradual resorption of pericardial and pleural fluid. He was discharged after sixteen months, returned to work and felt well for the next fourteen months.

At that time he developed a fever and cough and noted that he was losing weight. He returned to the hospital and was found to have active pulmonary tuberculosis in the left upper, right upper and right middle lobes with cavitation in the right apex. There was no evidence on physical examination or radiologically of pericardial disease. He died eight months later, thirty-nine months after the onset of his pericarditis. Postmortem examination was not performed.

Group III. This group consisted of three patients treated with streptomycin.

CASE I. E. C., a twenty year old colored woman, entered the hospital on May 3, 1948, complaining of shortness of breath. Her present illness had begun three weeks previously with pain in the interscapular area, followed soon with exertional dyspnea and then orthopnea. There was no history of previous serious illnesses or exposure to tuberculosis.

On examination she was found to be in her fifth month of pregnancy. Her temperature was 100°F., pulse 124, respirations 28 and blood pressure 114/70 with pulsus paradoxus. She was mildly dyspneic. The heart was questionably enlarged but the sounds were decreased in intensity and a loud pericardial friction rub was heard. There was no evidence of cardiac failure.

White blood count was 6,500 with 79 per cent polymorphonuclears. The hemoglobin was 11.5 gm. per cent. The urine was negative. The electrocardiogram showed changes suggestive of acute pericarditis. X-ray studies revealed an enlarged cardiac shadow with straightening of

the left border. Pulsations were markedly diminished. On June 10th a pericardial tap was done and 100 cc. of yellow fluid removed. Microscopic examination revealed 16,900 red blood cells and 3,900 white blood cells per cubic millimeter of which 88 per cent were lymphocytes. Acid-fast bacilli were seen on a smear.

On June 14th streptomycin (0.5 gm. intramuscularly twice daily) was started. By July 6th the patient was afebrile. On July 24th she continued to be asymptomatic and her cardiac silhouette became progressively smaller. On September 9, 1948, after thirteen weeks of streptomycin treatment, the drug was discontinued and on September 22nd the patient was discharged from the hospital.

She was followed up in the outpatient department and did well without special treatment. On July 13, 1949, a chest film revealed further diminution in heart size. On October 24, 1949, she was readmitted to the obstetrical service and delivered a normal infant.

On March 25, 1951, thirty months after treatment, she was entirely well. She did her own housework, took care of her children and worked out two days a week. The electrocardiogram and teleoroentgenogram were normal.

Case II. W. G., a twenty year old colored porter, entered the hospital on June 4, 1948, complaining of chest pain of five days' duration. His present illness began nine days prior to entry with pain in the interscapular area. Later an unproductive cough developed, exertional dyspnea and finally orthopnea. There was no history of exposure to tuberculosis or other previous serious illnesses.

On examination he appeared acutely ill with a temperature of 103.4°F., pulse 90, respirations 20 and blood pressure 122/90. Pulsus paradoxus was present. The heart was enlarged to the left and right; the sounds were distant; a loud pericardial friction rub was present. The neck veins were distended and there was questionable enlargement of the liver.

Blood and urine examinations were not remarkable. Roentgenography and fluoroscopy of the chest revealed a symmetrically enlarged cardiac shadow with markedly diminished pulsations. Pressure in the antecubital vein was 240 mm. of water. The arm to tongue circulation time by the decholin method was thirty seconds. A pericardiocentesis was performed the day of admission and 1,100 cc. of hemorrhagic, non-clotting fluid was removed. It contained 660,000 red blood cells and 6,000 white blood cells per cubic millimeter, of which 70 per cent were lymphocytes. Tubercle bacilli were demonstrated by smear, culture and guinea pig inoculation. Smear and culture of the sputum and pleural fluid were negative. An electrocardiogram revealed changes consistent with chronic pericarditis.

On June 10th streptomycin (0.5 gm. intramuscularly twice daily) was commenced. He improved gradually, becoming afebrile on September 4th. He was discharged on October 22, 1948, having received 112 days of streptomycin treatment. At that time he felt well. His pleural effusion had disappeared although fluoroscopically there was evidence of a small pericardial effusion.

He reported for a check-up on April 12, 1951, nearly thirty-one months after the cessation of streptomycin therapy. He felt entirely well and was employed as a truck driver. His physical examination was negative, his electrocardiogram and teleoroentgenogram of the chest normal.

Case III. J. C., a forty-five year old colored man, entered the hospital on January 9, 1949, complaining of shortness of breath of two weeks' duration. He had had a cough for the preceding two months, with production of sputum which was occasionally blood-tinged. He also complained of chest pain, headache, weakness and weight loss of about 14 pounds. He had no known exposure to tuberculosis but had been a sand mixer in a foundry for three years.

Physical examination revealed a thin, dyspneic man whose temperature was 102°F., pulse 90, respirations 24 and blood pressure 110/70 with obvious pulsus paradoxus. The area of cardiac dullness as measured by percussion was greatly increased; the sounds were distant. A pericardial friction rub was heard. There was distention of the neck veins. Rales were present at the lung bases.

The blood and urine examination were not remarkable. The sputum contained no acid-fast organisms. Pressure in the antecubital vein was 130 mm. of water. The arm to tongue circulation time was seventeen seconds, as measured by the decholin method. Cardiac fluoroscopy revealed a generally enlarged heart shadow with absent pulsations. A pericardial tap on January 9th yielded 75 cc. of serosanguineous fluid which contained 15,000 red blood cells and 2,100 white blood cells per

cubic millimeter of which 88 per cent were lymphocytes. Acid-fast organisms were seen on the smear. A guinea pig inoculated at this time and autopsied weeks later showed evidence of tuberculosis. The patient's tuberculin test was positive. The electrocardiogram showed changes consistent with pericarditis. Angiocardiograms on January 22nd demonstrated a large pericardial effusion although only 35 cc. of fluid could be secured that day by aspiration.

On January 26th the intramuscular administration of streptomycin was begun and continued for ninety days. The dose was 0.5 gm. twice a day.

On March 12th fluid was demonstrated in the right pleural cavity. On March 18th, during the seventh week of therapy, he became afebrile. On May 9, 1949, two weeks after the completion of streptomycin therapy, he was discharged without complaints and without any abnormal physical findings. The pleural effusion had practically disappeared and the cardiac silhouette was becoming progressively smaller. His chest film on September 13, 1949, revealed minimal obliterative pleuritis at both costophrenic angles and further diminution in the size of the cardiac silhouette. Cardiac fluoroscopy on October 27, 1949, was normal and an electrocardiogram taken on October 29, 1949, was also normal.

Twenty-four months after discontinuance of streptomycin he was working as a janitor. He felt entirely well. His physical examination, cardiac silhouette and electrocardiogram were within normal limits.

CONCLUSIONS

1. The clinical entities of primary tuberculosis of the pericardium and miliary tuberculosis with pericardial involvement are often indistinguishable when the patient is first seen.

2. Tuberculosis of the pericardium may heal spontaneously.

3. Death in patients with untreated tuberculosis of the pericardium is perhaps more often due to dissemination of the tuberculous infection than to pericardial involvement *per se*.

4. The administration of streptomycin improves the prognosis of tuberculous pericarditis although the long-term results cannot be properly evaluated at this time.

SUMMARY

1. Three patients with clinically primary tuberculous pericarditis have been treated with streptomycin for ninety, ninety and 112 days each, respectively. The duration of fever following admission to the hospital was thirteen weeks, as compared with twenty-one weeks in four patients whose pericarditis healed spontaneously without the aid of streptomycin. In the treated cases streptomycin was not given until the patients had been in the hospital two weeks or longer. The three treated patients are entirely well and leading normal lives at an average of twenty-eight months after the cessation of fever.

2. Of nine patients with clinically primary tuberculous pericarditis not treated with streptomycin five died within a few months of miliary spread of the tuberculosis or of cardiac failure. Spontaneous healing of the pericarditis occurred in the other four, but after an average asymptomatic period of 16.5 months tuberculosis appears elsewhere in the body.

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Effects of Mercurial Diuresis in Patients with Ascites Due to Cirrhosis*

JAMES G. HILTON, M.D.†

with the technical assistance of Helen Kalinsky

New York, New York

THERE is general agreement that in the normal subject as well as in the edematous patient the renal excretion of electrolytes following the injection of a mercurial diuretic consists predominantly of sodium and chloride.[1–8] It has also been noted that the amount of chloride in the urine on diuretic days often exceeds the amount of sodium to a slight degree.[2,4,6,8] In some instances variable increases in potassium excretion have been reported.[1,2,6,8,23]

Edematous patients may, during the course of mercurial diuresis, excrete large quantities of salt and water. For this reason the suggestion has been made that the occasional appearance of such symptoms as weakness, drowsiness, prostration, anorexia and cardiac arrhythmias following mercurial injections is due to the depletion of extracellular stores of sodium and chloride.[9–15] In most of these instances significant hyponatremia developed only in patients who were on a restricted intake of dietary salt, but it is of interest that a direct temporal relationship between symptomatology and the level of plasma sodium could not be established in some cases.[14] When there has been no salt restriction, mercurial diuretics have had little effect on plasma sodium and chloride concentrations in both the edematous patient and in the normal individual.[2,4,16–18,23]

The data to be reported in this study indicate that in cirrhotic patients with ascites the renal excretion of *potassium* following the administration of mercuhydrin may, under certain circumstances, be of such magnitude as to produce hypokalemia and a clinical state indistinguishable in symptomatology from the previously described low salt syndrome.

MATERIAL AND METHODS

Twenty-four-hour urine volume and sodium, potassium and chloride excretion were measured in nine experiments on eight patients with ascites due to cirrhosis of the liver. The daily dietary intake of sodium chloride was approximately 77 mEq. and that of potassium about 60 mEq. After a two-week control period during which no diuretics were given, mercuhydrin (2 cc. three times a week intramuscularly) was administered and continued for an average duration of three weeks. Following this 113 mEq. per day of ammonium chloride (uncoated tablets) were added to the diuretic regimen for an average duration of ten weeks. In most patients observations were extended to include a subsequent period of four weeks on mercuhydrin alone followed with a final two-week period of no diuretic therapy.

Arterialized venous blood samples[19] were obtained from each patient at approximately five-day intervals and analyzed for pH, carbon dioxide content, sodium, potassium and chloride. Plasma bicarbonate concentration was calculated from the pH and carbon dioxide content by means of the Henderson-Hasselbach equation, using a pK of 6.1 for carbonic acid.

In addition to these eight patients there were five cirrhotics with ascites and fifteen cirrhotics clinically free of ascites in whom only plasma electrolyte values were recorded during two- to four-week periods of no diuretic administration. The values obtained in the entire group of

* From the Research Service, First (Columbia University) Division, Goldwater Memorial Hospital, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. This study was supported in part by a grant from the Public Health Research Institute of the City of New York, Inc.

† Fellow, New York Heart Association.

cirrhotics were compared with those in thirty-four chronically ill patients with normal fluid balance variously diagnosed as having rheumatoid arthritis, arteriosclerosis, muscular dystrophy, multiple sclerosis and spastic paraplegia.

TABLE I

COMPARISON OF PLASMA ELECTROLYTES IN CIRRHOSIS AND IN NORMAL MAN

	Sodium			Chloride			Potassium		
	No.	Mean (mEq./L.)	Standard Deviation (mEq./L.)	No.	Mean (mEq./L.)	Standard Deviation (mEq./L.)	No.	Mean (mEq./L.)	Standard Deviation (mEq./L.)
Cirrhosis (ascites)	13	129.3	6.21	12	97.0	4.90	12	4.36	0.39
Cirrhosis (no ascites)	15	138.7	1.92	14	102.3	2.92	8	4.36	0.41
Normal	34	139.4	2.01	36	105.2	3.53	27	4.20	0.37

The chemical methods employed have been described in an earlier publication from this laboratory.[20]

RESULTS

In Table I plasma sodium, chloride and potassium concentrations in cirrhotic patients not receiving diuretics have been compared with a group of hospitalized patients in whom there were no disturbances in fluid or electrolyte excretion (designated normal). It is apparent that the patients with ascites exhibited significantly lower concentrations of sodium (m 129.3 mEq./L.) and chloride (m 97 mEq./L.) than did those who were edema free (m 138.7 and 102.3 mEq./L., respectively). The latter group did not differ from the normals in this respect. Although individual plasma sodium concentrations as low as 116 mEq./L. were recorded in the ascitic group, there was not one instance of any symptom complex suggestive of that which has been described as occurring in hyponatremia. The levels remained quite constant from week to week in any one patient and were unaltered by the abdominal paracenteses which were required for relief of ascites. Plasma potassium values in all three groups were within the accepted normal range.

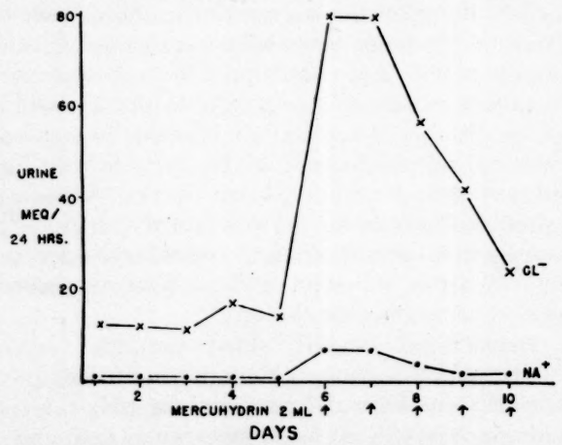

FIG. 1. Patient R. O. Effect of mercuhydrin injections (indicated by arrows) on twenty-four hour excretion of sodium and chloride.

Early in the course of the study it became apparent that most of the ascitic patients did not respond to mercurial diuretics, using weight loss as a criterion. This does not imply that all cirrhotics with ascites are refractory to mercurials, but merely that the particular patients studied, all of whom were transferred to this hospital for chronic care, represented an advanced stage in the disease in which mercurial diuretics alone were ineffective in controlling recurrent ascites formation. This lack of response in one of the patients is depicted graphically in Figure 1 from which it can be seen that the twenty-four-hour sodium excretion averaging less than 1 mEq. was only slightly increased by the administration of mercuhydrin for five consecutive days. Chloride output was consistently greater than sodium and the *relative* increase following the mercurial injections was large.

The mean values for water and electrolyte excretion in 136 samples of urine in control periods, 108 samples of urine from cirrhotics on days of mercurial injections and 201 samples of urine from cirrhotics on days of mercurial injections during the administration of ammonium chloride are tabulated in Table II. The average excretion of 3 mEq. per day of sodium and 9 mEq. per day of chloride during the control periods represents almost complete retention of dietary salt whereas the average potassium excretion of 62 mEq. closely approximated potassium intake. Mercuhydrin had essentially no effect on potassium output and its effect on

sodium and chloride was of slight to moderate degree. Little diminution in the rate of ascites formation was achieved by mercuhydrin alone in seven of the eight patients studied.

When 113 mEq. per day of ammonium chloride were added to the regimen of each patient, a marked potentiation in the mercurial responses occurred and persisted for as long as the salt was administered (up to thirteen weeks in some cases). Plasma pH and bicarbonate concentrations were low during the first week but returned to normal and remained so during subsequent weeks. Similar potentiation independent of plasma acid-base balance has also been observed in normal individuals and the possible nature of its mechanism has been discussed.[21] The most striking alteration in electrolyte excretion observed was a large increase in twenty-four-hour potassium output, the average amount excreted being 132 mEq. on each mercurial day. (Table II.) Some patients excreted as much as 250 mEq. in a single twenty-four-hour period, representing almost 8 per cent of their total body potassium.[22] From Table II it can be seen also that the sodium ion was present to the extent of only 50 per cent of the excreted chloride on the days of potentiated diuresis. It is apparent that increased excretion of potassium made up for part of this cation deficit, the remainder of which could well be accounted for by unmeasured ammonia.

TABLE II

EFFECT OF DIURETICS ON ELECTROLYTE EXCRETION IN PATIENTS WITH ASCITES DUE TO CIRRHOSIS

Therapy	No. of Observations	Volume (ml./24 hr.)	Sodium (mEq./24 hr.)	Potassium (mEq./24 hr.)	Chloride (mEq./24 hr.)
None	136	698	3	62	9
Mercuhydrin	108	1350	45	70	78
Mercuhydrin plus ammonium chloride	201	3255	185	132	389

TABLE III

FALL IN PLASMA POTASSIUM LEVELS* DURING PHASE OF POTENTIATED DIURESIS

Patient	No Therapy (2 wk.-mEq./L.)	Mercuhydrin (3 wk.-mEq./L.)	Mercuhydrin plus Ammonium Chloride		Mercuhydrin (4 wk.-mEq./L.)	No Therapy (2 wk.-mEq./L.)
			Lowest (3rd wk.-mEq./L.)	Average (10 wk.-mEq./L.)		
R.I.	5.48	4.78	3.60	3.94	....	5.03
M.O.	4.40	3.71	2.75	3.34	4.13	4.03
S.M.	4.20	3.71	2.39	3.07	....	4.58
C.O.	4.17	3.84	3.04	3.43	4.29	4.20
R.A.	4.16	4.27	3.50	3.82	4.43	4.16
D.O.	4.12	4.42	2.94	3.27	....	....
W.A.	4.11	3.93	2.75	3.27	4.09	4.16
S.M.	4.06	4.25	2.25	3.36†	4.10	4.15
S.E.	3.42	3.15	2.35	3.04	3.14	3.44
Mean	4.23	4.01	2.84	3.39	4.03	4.22

*With the exception of the lowest values, which are singly tabulated, the data represent averages of 3 or more determinations from each patient during each period.

†Received supplementary KCl, 80 mEq./day for 1 wk.

During this period of diuresis weight losses ensued in all patients and the intervals between paracenteses were greatly prolonged. An example of this effect is shown in Figure 2.

In Figures 2 and 3 complete data on electrolyte excretion from two representative patients have been charted together with plasma values during the different phases of therapy. The potentiating effect of ammonium chloride

on mercuhydrin is evident, and from Fig. 2 it can be seen that this effect persists despite return of the plasma bicarbonate concentration to normal. During the phase of diuresis there was marked retention of electrolyte on the days no mercurial was administered. At such times values and 28 mEq. per day during the remaining period. It appears, therefore, that no change in renal retention occurred which could account for this phenomenon. Fecal excretion was not measured, nor was dietary intake sufficiently standardized to permit any calculation of over-

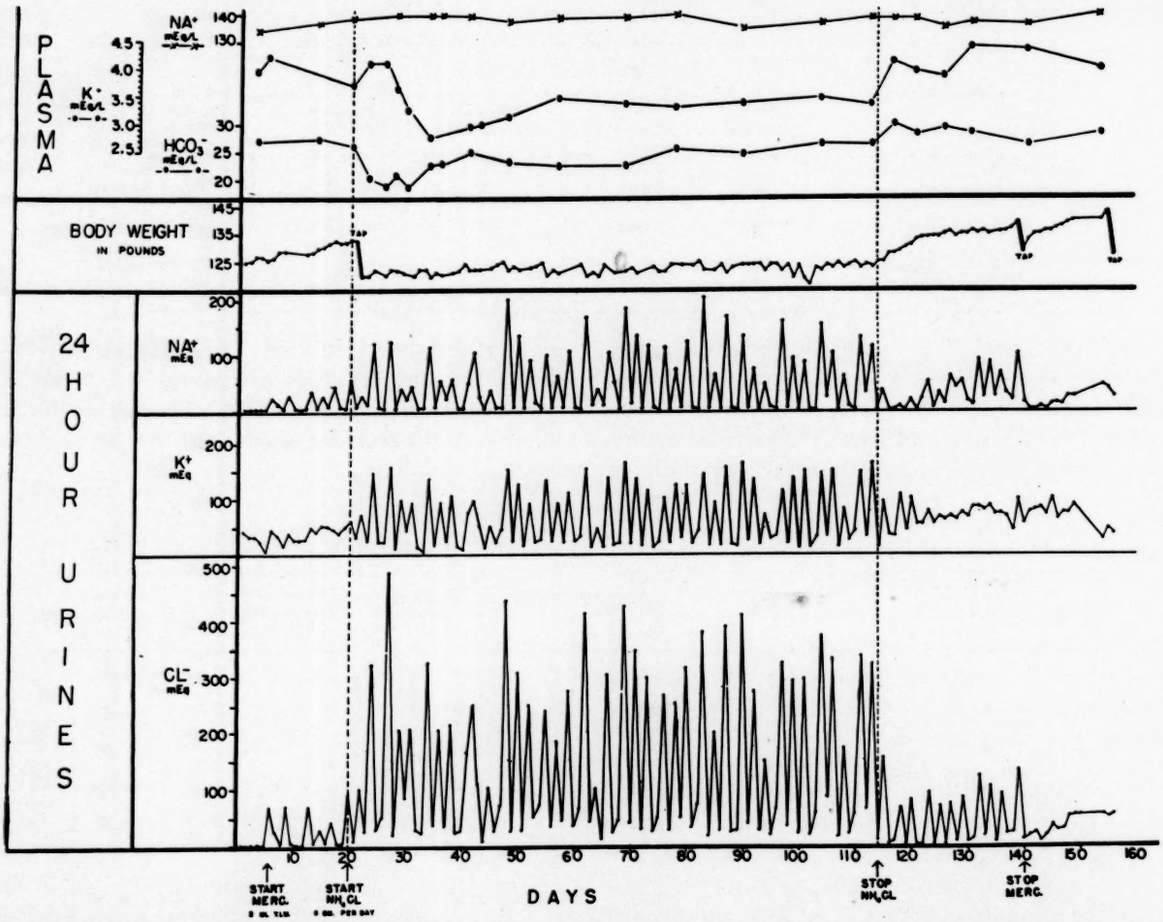

FIG. 2. Patient W. A. Effect of 113 mEq. (6 gm.) ammonium chloride per day in enhancing the diuretic response to mercurial injections (given three times a week). Excretion of chloride on mercurial days during this period greatly exceeded that of sodium. Potassium excretion was also markedly increased. On non-mercurial days it can be seen that the output of these electrolytes was greatly decreased. Plasma bicarbonate concentration was unchanged except for the acidosis initially following administration of the salt. Note the fall in plasma potassium levels in conjunction with potassium diuresis. A slight rise in plasma sodium concentration was also observed during the phase of potentiated injections. This patient had required seventeen abdominal paracenteses at three-week intervals prior to the combination of mercuhydrin and ammonium chloride.

potassium U/P ratios of less than 1 were frequently observed.

In all patients studied there was a fall in plasma potassium concentrations concomitant with potassium diuresis. However, the lowest values were recorded early in the third week of increased excretion and then subsequently rose slightly and leveled off. (Figs. 2 and 3.) Potassium excretion on non-mercurial days averaged 26 mEq. per day up to the time of lowest plasma all balances. Increased appetite with increased intake of dietary potassium might well have been an important factor in this subsequent rise in the plasma concentrations.

The extent of fall in plasma potassium during the different phases of therapy is tabulated in Table III. It is apparent that there was very little change except during the period of potentiated injections. By the third week of ammonium chloride administration the mean level for the

group had reached its lowest point (2.84 mEq./L.). The group average for the entire ten-week period was slightly higher, however (3.39 mEq./L.). Upon discontinuance of ammonium chloride and the cessation of potassium losses there was prompt return of plasma values to control levels despite continuation of the mercurial injections. In two patients, S. M. and S. E., symptoms of weakness, drowsiness, anorexia and marked prostration developed at a time when their plasma potassium concentrations were 2.25 and 2.35 mEq./L., respectively. Simultaneously recorded plasma sodium, chloride and bicarbonate concentrations were normal. In one patient relief occurred within eight hours following the oral administration of 80 mEq. of potassium chloride (2 gm. three times a day); in the other a similar improvement was brought about upon prevention of further potassium losses by discontinuance of the ammonium chloride.

In none of the eight subjects studied was any fall noted in plasma sodium or chloride concentrations below those observed during the control periods. Actually, in four patients the values, low to begin with, were consistently higher during the phase of diuresis than at any other time (average plasma sodium increase +6.5 mEq./L.).

Electrocardiograms taken during the hypokalemic phase showed prolonged Q-T intervals (six cases), low amplitude T waves (three cases) and S-T depression (one case). All these effects were reversible and disappeared upon return

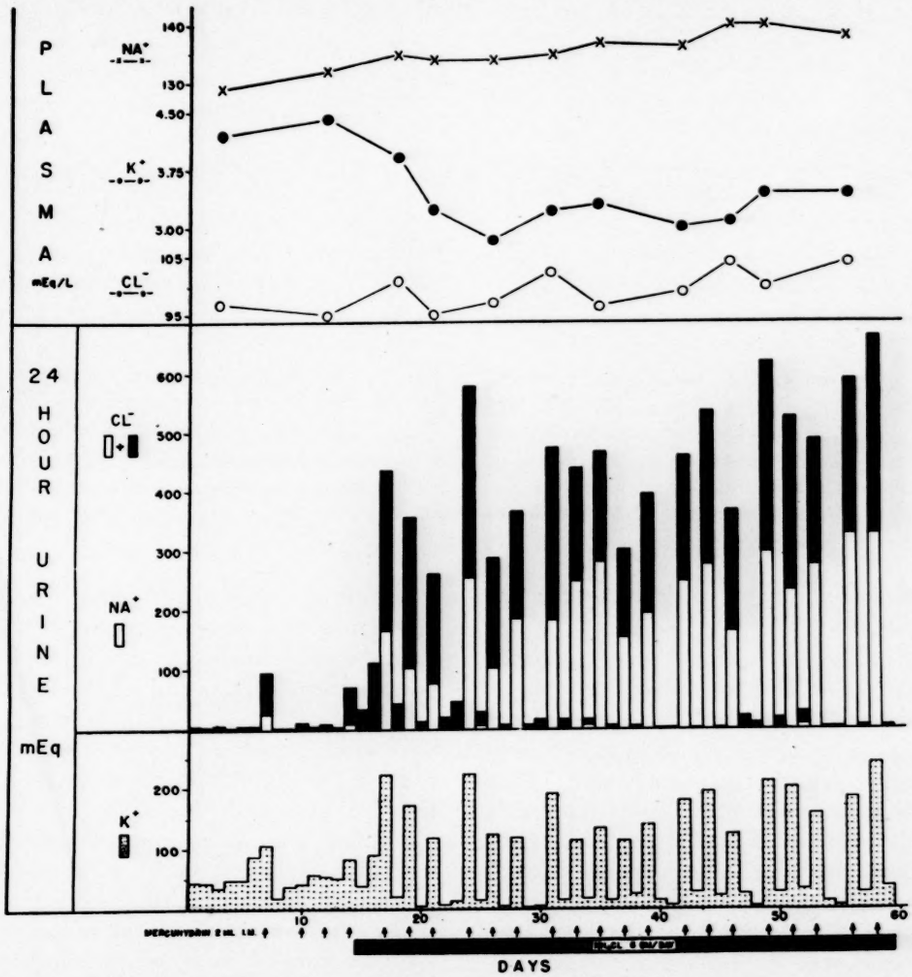

FIG. 3. Patient D. O. The features of this figure are the fall in plasma potassium and rise in plasma sodium concentrations occurring upon institution of the phase of potentiated diuresis. Note also during this period the large amounts of potassium excreted on mercurial days (indicated by the arrows) and the almost complete retention on other days.

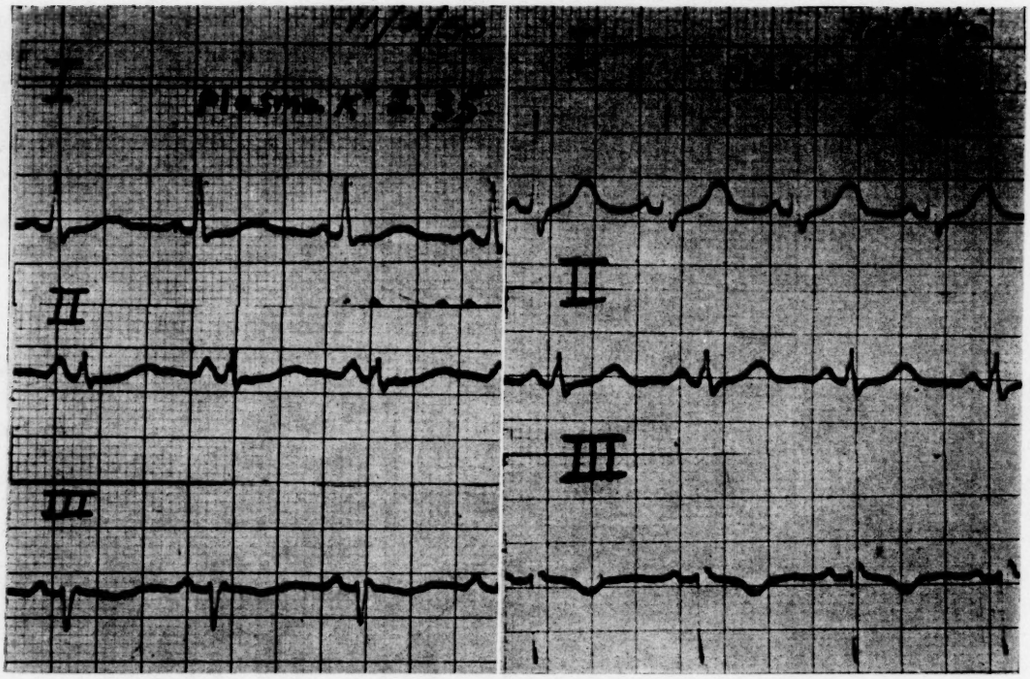

FIG. 4. Patient S. E. Standard limb lead electrocardiograms. At the time of hypokalemia the Q-T interval in lead I measures 0.40 sec., there is S-T depression in leads I and II and the T waves are of low amplitude in all leads.

of the plasma potassium concentrations to normal. (Fig. 4.)

COMMENTS

Potassium excretion in normal subjects following mercurial administration is usually unaltered or only slightly increased.[1,2,7,21] This also holds for edematous individuals in whom the natriuretic response is good.[4,5,24] Significant potassium losses, however, have recently been observed in association with the excretion of large amounts of chloride.[6,8,23] Because the periods of study were of short duration, hypokalemia did not occur in these cases.

When the output of sodium following a mercurial injection is small relative to chloride, it is apparent that potassium appears in the urine in increased amounts. During the phase of potentiated diuresis the twenty-four-hour excretion of chloride was twice that of sodium. Increased excretion of potassium accounted for a large part but not all of this cation deficit. The remainder was undoubtedly made up mainly by unmeasured ammonia although the presence of increased amounts of calcium and magnesium[1,2] cannot be ruled out.

During this period the average excretion of 132 mEq. of potassium on each mercurial day was well in excess of the dietary intake for that day. In several diureses the output was greater than the total calculated amount of extracellular potassium so that actual intracellular loss seems unquestionable. It is not surprising, therefore, that some degree of hypokalemia developed in each of the eight patients studied. The diminution in excretion occurring on the days no mercurial was given undoubtedly limited the extent of depletion and helped stabilize plasma potassium levels. It appears unwarramted to make the assumption that negative potassium balance existed in these patients for any prolonged period solely from the data on urinary excretion. Even though potassium output on mercurial days remained high throughout the entire phase of potentiated diuresis, a small increase in the daily dietary intake would be sufficient to maintain *weekly* balance and could well account for the plasma levels subsequently stabilizing at slightly higher values than the lowest observed. Moreover, decreases in the unmeasured fecal excretion could also have occurred as a compensatory mechanism for the increased renal excretion, and th's too would tend to offset any negative balance over prolonged periods. In the absence of complete balance data, therefore, any estimation of the

nature or degree of potassium balance cannot be made.

Although chloride loss in the diuretic urine was large, its concentration was only slightly higher than that of the extracellular fluid. In every instance, however, plasma chloride concentrations were within normal limits during the phase of ammonium chloride administration. This again is most likely a reflection of the decreased excretion occurring on non-mercurial days.

With regard to sodium, the excretion of a large volume of fluid containing only 57 mEq./L. of this ion (calculated from Table II) could conceivably be a factor in the observed rise in plasma sodium concentrations which occurred in four of the eight patients. The low plasma values seen in the group with ascites during periods of no diuretic therapy is not easily explained. It may be that some anti-diuretic substance[25,26] is present in these patients which causes the retention of water and salt in hypotonic concentrations and so leads to dilution of the extracellular fluid with respect to these ions. Such an altered tonicity of body fluids, however, was without apparent untoward effect on the general clinical condition.

In view of the data presented it is evident that the development of a syndrome consisting of weakness, prostration, drowsiness and anorexia in patients undergoing diuresis should not necessarily be attributed to hyponatremia unless it can be shown that there is no loss of potassium which could account for the symptoms. This is particularly pertinent with respect to cardiac patients who may be receiving digitalis. Potassium loss following mercurials could well account for many of the untoward signs which in the past have been attributed to the mobilization of digitalis from edema fluid,[27–29] especially in the light of recent observations indicating a relationship between digitalis toxicity and the potassium content of cardiac muscle.[30–32]

SUMMARY

The plasma concentrations of sodium and chloride in thirteen patients with ascites due to cirrhosis averaged 129.3 and 97.0 mEq./L., respectively. Such altered tonicity of extracellular fluid was unassociated with any untoward symptoms or signs.

These patients were further characterized by their almost total inability to excrete dietary sodium chloride and their lack of response to mercurial diuretics.

Good diuretic effects were obtained from mercuhydrin when ammonium chloride in a dose of 113 mEq./day was administered. This potentiation was independent of plasma acid-base balance. The twenty-four-hour sodium excretion under these conditions was only one-half that of the chloride. Potassium output on these days was greatly increased, some patients excreting as much as 250 mEq. in a single twenty-four-hour period.

Hypokalemia occurred in all patients during the phase of potassium loss and, in some, symptoms of anorexia, drowsiness, weakness and prostration developed. Plasma sodium and chloride concentrations were at normal levels at the time such symptoms were noted. The excretion of large amounts of fluid hypotonic with respect to sodium is considered a factor in the rise in plasma sodium concentrations which occurred in some patients during the phase of diuresis.

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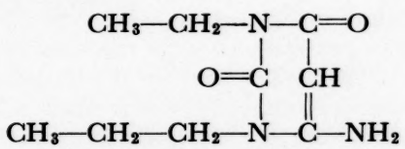
Clinical Observations on a New Oral Diuretic 1-Propyl-3-Ethyl-6-Aminouracil and Preliminary Studies on 1-Allyl-3-Ethyl-6-Aminouracil*

A. KATTUS, M.D., T. M. ARRINGTON, M.D. *and* E. V. NEWMAN, M.D.
Los Angeles, California *Cascade, Maryland* *Baltimore, Maryland*
with the technical assistance of Marion Birmingham, Margot Robinson and Mary Larcombe

In the hope of finding a potent, non-toxic oral diuretic drug, thirty-four compounds chemically related to the xanthines were tested for diuretic activity in dogs.[1] Several compounds containing the xanthine nucleus were shown to have highly potent diuretic activity but these were also emetic. Compounds derived from the uracil nucleus produced a low order of gastrointestinal disturbance and one of them, 1 propyl-3-ethyl-6-aminouracil, showed good diuretic potency although not as great as some of the xanthines. This compound was submitted to clinical trial by oral administration, the results of which are herein presented.

The compound was synthesized by Papesch and Schroeder[2] and is hereafter referred to by its serial number 2614. Its structural formula is shown as follows:



1-propyl-3-ethyl-6-aminouracil

Chronic Toxicity in Dogs. Before instituting studies in humans, chronic toxicity studies were carried out in dogs. Six mongrel dogs were given 2614 in daily doses of 50 mg. per kilo for ten days. The maximum human dose has been 25 mg. per kilo per day. During the test period two of the dogs showed mild anorexia; the others remained well and active. There was augmentation of urine volume and sodium excretion during the first two or three days of drug administration but in subsequent days these values returned to pretreatment levels. Determinations of hematocrit, leukocyte count, differential leukocyte count, routine urinalysis and phenolsulfonphthalein excretion were made before and after the ten-day period of drug administration. No significant difference between the pretreatment and post-treatment values of these tests was exhibited in any of the dogs. At the end of the test period all dogs were sacrificed and histologic study of the liver, kidneys and adrenals was carried out. No evidence of tissue damage due to the drug could be detected although two of the animals showed lesions of chronic pyelonephritis.

Mode of Action. In Figure 1 is illustrated an experiment on a female dog in which 1 gm. of 2614 was infused intravenously in the space of fifty minutes after twenty minutes of control observations. Glomerular filtration rate was measured by clearance of exogenous creatinine and renal plasma flow by clearance of para-aminohippurate administered by constant intravenous infusion. Urine collections were made through an indwelling catheter at intervals of from ten to thirty minutes. Clearance of sodium and potassium was followed along with urine flow, glomerular filtration rate and renal plasma flow. The graph shows the marked augmen-

* From the Department of Medicine of the Johns Hopkins University School of Medicine and Hospital, Baltimore, Md. This work was supported by a grant from G. D. Searle Company and in part by the Life Insurance Medical Research Fund.

tation of sodium chloride excretion brought about by the infusion of 2614 despite a decrease in glomerular filtration rate. Potassium excretion, which is not charted, showed a much smaller increase. These data suggest a specific inhibitory effect by the drug on the tubular

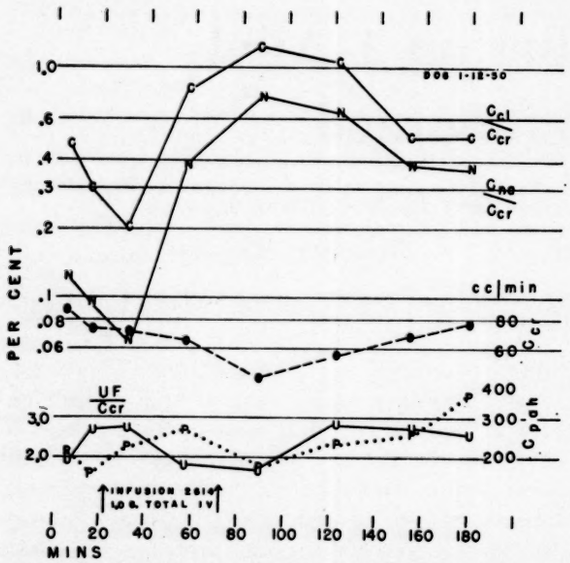


FIG. 1. Effect of intravenous infusion of 2614 into a female dog. N = sodium, C = chloride, U = urine flow, P = clearance of para-aminohippurate. Excretion of sodium, chloride and water are expressed as the per cent of filtered material which is excreted. This value is obtained by dividing the clearance of the material by the filtration rate. In the case of water the urine flow in cc./minute is divided by the filtration rate. Potassium excretion which is not charted doubled during drug infusion while sodium excretion showed a tenfold increase.

reabsorption of sodium and chloride. The fact that the urine volume did not increase during the period of this experiment suggests that augmented salt excretion is the primary means by which diuresis is achieved and that the urine volume increase follows.

The significance of the drop in glomerular filtration rate is not clear. It did not occur in three other dogs similarly tested.

CLINICAL MATERIAL AND METHODS

Initially, 2614 was given to a series of non-edematous male patients hospitalized for care of chronic illnesses. None of these patients had evidence of circulatory insufficiency and all had normal renal function as determined by urinalyses and phenolsulfonphthalein excretion tests. All had been in the hospital for at least a month and all consumed as much as they wished of the regular hospital diet. Salt and water were allowed *ad libitum*.

The test procedure in the non-edematous subjects consisted of a six-day period of observation during which all urine was collected in twenty-four-hour periods beginning at 9 A.M. The test drug was administered on the fourth day. Urine volume and sodium excretion were measured for each day. Sodium and potassium were determined by flame photometry. Urinalysis and phenolsulfonphthalein tests were made in all subjects before and after the six-day test period.

In the first experiment 2614 was administered to three patients in order to confirm the diuretic activity of the drug in humans. In the next four experiments ten subjects were employed to compare the effect of 2614 with thiomerin and with aminophyllin and also to test the effect of a larger dose of 2614. The effect of a close chemical relative of 2614 was also tested in this series of experiments.

Therapeutic trials with 2614 were undertaken in edematous hospital patients. The only criterion for their selection was the presence of pitting edema. They fell naturally into three groups, those with congestive cardiac failure, those with renal disease and those with cirrhosis of the liver. All patients were on low salt diets containing a maximum of 2 gm. of sodium chloride per day. All urine was collected in twenty-four hour periods, the periods beginning each morning at 9 A.M. Sodium and potassium content of the urine was determined on a flame photometer. Patients were weighed daily. Although several days of control observations prior to instituting drug therapy were desired, it was sometimes necessary to limit the control period to one or two days because of the severity of the patient's illness; 2614 was always administered in capsules containing 250 or 300 mg. which were taken four times a day, one after each meal and one at bedtime.

In the earlier tests drug administration was limited to one day at a time. Later three-day test periods were employed and subsequently the periods of administration have been extended to four or five days.

Recently some patients have been continued for as long as four or five weeks of continuous administration while being followed in the outpatient department. Many of the patients have had several courses of drug administration.

EFFECT IN NON-EDEMATOUS SUBJECTS

In order to establish the drug's diuretic activity in human beings it was first administered to three non-edematous male subjects in four doses of 300 mg. each given at intervals of four hours beginning at 9 A.M. on the test day. The results are shown in Table 1. The marked increase in urine volume and sodium excretion on the test day confirmed the diuretic activity of the drug in human beings. The response in these three subjects was commensurate with the values recorded by Blumgart and his associates[3] when they studied the effect of mercurial diuretics on normal subjects.

TABLE 1

EFFECT OF 2614 IN THREE NON-EDEMATOUS SUBJECTS

Subject	Urine Volume Control cc./day	Urine Volume Drug Day cc./day	Na Excretion Control mEq./day	Na Excretion Drug Day mEq./day	Potassium Excretion Control mEq./day	Potassium Excretion Drug Day mEq./day
K	1366	2095	155	304	55	71
B	2272	2810	250	407	83	99
P	1280	1800	128	300	36	61

An experiment was then set up in which ten non-edematous male subjects were tested with one day's administration of 2614 in four doses of 300 mg. each given at four-hour intervals beginning at 9 A.M. The results are shown in the top line of Figure 2.

Eight of the ten subjects so treated showed marked increase in urine volume and sodium excretion on the test day. One showed only a slight increase and the other showed no increase. For all ten subjects the average sodium excretion on the test day was 193 per cent of the mean control while potassium excretion on the test day was 136 per cent of the mean control. Three of the patients complained of slight gastric discomfort but all ate full meals.

One month later the same ten patients were tested in a similar manner but in this experiment half the group were given a larger dose of 2614 while the other half were given 1, 3-dipropyl-6-aminouracil (serial number 2588), a close chemical relative of 2614. In the first half of line 2 in Figure 2 are shown the results of administration of 500 mg. of 2614 four times during the test day. All five of the patients complained of gastric discomfort but none vomited. On this larger dosage there was less increase both in urine volume and sodium excretion than with 300 mg. four times a day. The one patient who had failed to respond to the smaller dose also failed to respond to the larger dose. This test would seem to indicate that the optimal dose is in the neighborhood of 1 gm. per day for an adult. The other five patients on this occasion were given compound 2588 in doses of 0.3 mg. four times during the day. As shown in the second half of line 2 in Figure 2 no diuretic response resulted, thus indicating the high degree of specificity of the chemical structure of 2614 for the pharmacologic action of the drug.

Again following the lapse of one month the same ten subjects were tested. On this occasion each of the subjects were given 2 cc. of thiomerin subcutaneously on the morning of the test day. Results are shown at the bottom of Figure 2. Average sodium output on the test day was 179 per cent of the mean control, thus indicating that orally administered 2614 has a diuretic potency comparable to the effect of a parenterally administered mercurial in normal subjects. It should be noted that subjects D. and H. responded more vigorously to 2614 than they did to the mercurial while subject V., who failed to respond to 2614, did respond vigorously to the mercurial. Subject G. responded poorly to both drugs.

A final test on these ten subjects was carried out at a later date when they were given aminophyllin orally in doses of 0.3 gm. four times on the test day. The results which are not illustrated, showed sodium output on the test day to be 136 per cent of the mean control.

Urinalysis and phenolsulfonphthalein excretion tests were carried out in each patient

before and after each experiment. In no case was there any significant alteration between the pretreatment and post-treatment values of these tests.

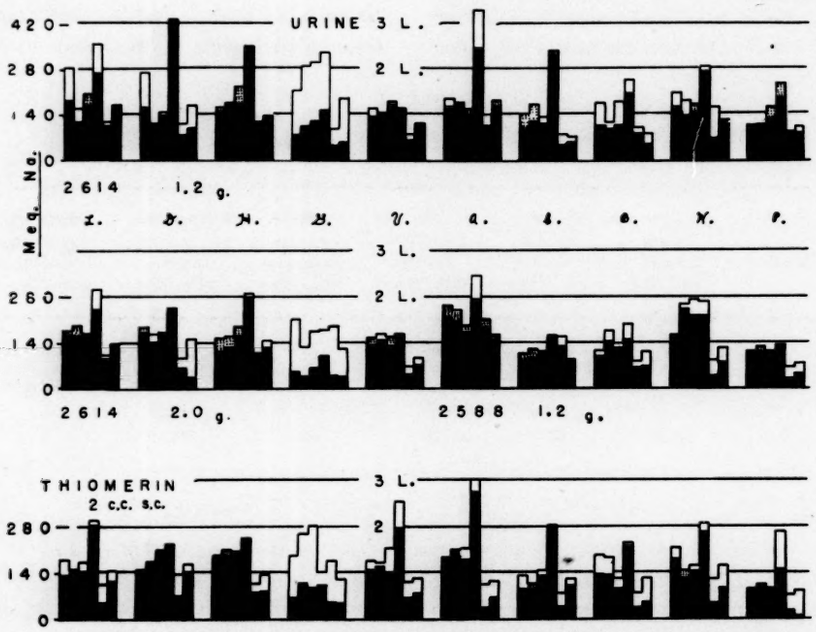


FIG. 2. The effect of 2614 in non-edematous subjects. Each vertical bar represents twenty-four-hour urine volume and sodium excretion. Urine volume is plotted from the base line to the top of the clear area in liters. Sodium is shown in black in mEq. plotted so that 140 mEq. of sodium falls at the same level as 1 L. of urine volume. The stippled areas indicate that the sodium level exceeded the urine level so that urine contained more than 140 mEq. of sodium per L. Drug was given on day 4; days 5 and 6 are follow-up days. The top line shows effect of 2614 (300 mg. four times a day) given on the fourth day after three days of control observations. The middle line shows the effect of 2614 (500 mg. four times a day) given on day 4 to the first five subjects. The last five subjects received 1,3,-dipropyl-6-aminouracil on day 4. The bottom line shows effect of thiomerin 2 cc. subcutaneously given at 9 A.M. on day 4.

THERAPEUTIC EFFECT IN EDEMATOUS PATIENTS

Method of evaluation. Pertinent data on the patients and results are presented in Table II. It will be seen that in most instances administration of the drug was accompanied with marked increase in urine volume and sodium excretion with concomitant loss of weight. However, when attempt is made to set up criteria whereby the degree of diuretic activity of the drug may be estimated, many difficulties are encountered. Study of Table II reveals that most of the patients showed wide variation in their responsiveness to the drug at various times. This is to be expected since the quantity of edema was lessening with each course of the drug. It is also apparent that percentile values for data of test days over data of control days cannot be used with respect to urine volume and sodium excretion because some patients had such low control excretion values that doubling or tripling these values would still not constitute a therapeutic response. It is also apparent that no single measurement alone will provide the criterion since some patients lost more water than they did sodium; some did just the opposite. In some the weight loss seemed to be more closely related to sodium loss while in others it seemed to follow the urine volume, such factors possibly being contingent upon alterations in extracellular electrolyte concentrations. It would appear that any valid index of diuretic response to a drug will have to be based on the absolute values of the changes in all three measurements: weight, urine volume and sodium excretion. Fortunately, in most instances these factors did seem to parallel one another with good consistency.

Employing the three measurements of weight loss, urine volume and sodium excretion we

TABLE II

DATA ON THIRTY-SEVEN PATIENTS TREATED WITH 2614

Case No.	Patient, Race, Sex, Age, Diagnosis	Date Drug Course Started	Dose gm./day	Duration of Drug Course (days)	Weight Change, Control Period (lb.)	Weight Change, Drug Period (lb.)	Urine Volume, Control Period (cc./day)	Urine Volume, Drug Period (cc./day)	Na Excretion Control Period (mEq./day)	Na Excretion Drug Period (mEq./day)	Diuretic Response Index	Remarks
					Congestive Heart Failure							
1	R.L., C. M., 54	9/24/49	1.2	1	-2.5 (1)*	-4.5	2000 (1)	4270	123 (1)	422		
	Syphilitic aortic	10/4/49	1.2	1	-2 (1)	-1.5	2230 (1)	3225	69 (1)	118		
	insufficiency	10/13/49	2.0	1	+1.5 (1)	-1.0	2780 (1)	2700	60 (1)	90	3	
2	G.M., C. F., 38	10/13/49	1.2	1	-1 (1)	-3	1860 (1)	2380	52 (1)	154	2	
	HCVD											
3	E.S., W. F., 45	10/15/49	0.5	1	0 (1)	+3	680 (1)	600	5 (1)	3		Vomiting
	RHD	10/18/49	1.0	1	+1 (1)	0	2270 (1)	2400	12 (1)	24		No vomiting
		10/21/49	1.0	1	-.5 (1)	-.5	2300 (1)	2210	13 (1)	47	0	No vomiting
4	R.W., C. M., 59	12/6/49	1.2	1	-2 (2)	-4	570 (2)	1600	10 (2)	41		
	ASHD	12/15/49	1.2	4	+1 (3)	-15.5	867 (4)	2104	38 (4)	158		
		12/28/49	1.2	3	-4 (3)	-11.5	1770 (3)	2393	128 (3)	200	3.3	
5	G.B., W. M., 49	12/11/49	1.2	1	+.5 (1)	+1	560 (1)	555	3 (1)	2		
	HCVD	12/18/49	1.2	3	-3 (3)	-4	648 (3)	2055	13 (3)	112		
		12/28/49	1.2	4	+3 (4)	-3	660 (1)	1941	8 (4)	73	2	
6	A.R., W. F., 69	1/1/50	1.2	1.5	+1 (2)	-.5	230 (2)	250	2 (2)	0.5	0	
	ASHD											
7	E.R., C. M., 47	1/9/50	1.2	3	-1 (3)	-11	930 (1)	1786	66 (1)	170	2.7	
	HCVD obesity											
8	C.B., C. M., 51	1/24/50	1.2	4	-2 (4)	0						Incontinent
	HCVD											
9	E.C., W. F., 37	1/25/50	1.2	4	-.5 (1)	0	390 (1)	455	2 (1)	2		
	RHD	2/2/50	1.2	3		0	607 (3)	773	1 (3)	2		
		3/5/50	1.0	3	+1 (3)	-2	948 (3)	823	2 (3)	1	0	
10	J.A., W. M., 46	1/25/50	.5	1	0 (1)	0	1730 (1)	3607	184 (1)	232	1.3	
	RHD											
11	G.C., C. M., 48	1/25/50	1.2	3	-1 (2)	-4 (3)	1190 (1)	1538	10 (1)	98		Thiomerin
	ASHD	2/3/50	1.2	3	0 (3)	-7	2180 (3)	2943	57 (3)	159		given on
		2/9/50	1.2	3	-2 (3)	-3.5	1332 (3)	1847	49 (3)	54	2.3	day 3
12	R.G., W. M., 63	1/26/50	1.0	5	-1/3 (3)	-6	2100 (3)	3130	68 (3)	151	2.3	
	ASHD											
13	J.S., W. M., 67	2/2/50	1.2	3	+1 (3)	-12.5	1125 (3)	2510	93 (3)	236		
	Arteriosclerotic heart disease	2/24/50	1.2	3	+2.5 (3)	-1.5	1500 (3)	1927	14 (3)	45	3	

TABLE II (Continued)

14	J.A., W. F., 30 HCVD	2/18/50	1.5	7	?	-9.5	550 (1)	1183	3 (1)	50	1.7	No control weight recorded; renal insufficiency
15	C.T., C. M., 68 Cor pulmonale	3/21/50	1.0	3	+2 (3)	-7	1210 (3)	2113	13 (3)	114	2.3	Nausea on 4th day
16	L.G., C. F., 59 Syphilitic AI	3/21/50	1.0	4	-7 (4)	-7	1274 (4)	2222	52 (4)	73		
		3/28/50	1.0	4	0 (3)	-5.5	2640 (3)	3555	62 (3)	76		
		4/3/50	1.0	4	+2 (3)	-3	2790 (3)	3637	30 (3)	40	1.3	
17	A.S., W. M., 37 HCVD	4/9/50	1.5	3	-3 (3)	-1	637 (3)	757	38 (3)	84		
		4/20/50	1.0	3	-0.5 (3)	-2	680 (3)	1160	22 (3)	40		
		4/25/50	1.0	2	0 (2)	0	885 (2)	955	33 (2)	45	1	
18	F.S., C. F., 43 HCVD	4/10/50	1.2	2	?	?	370 (2)	550	5 (2)	8	0	Nausea without vomiting
19	Y.P., W. M., 35 HCVD	4/14/50	1.0	3	+2 (2)	-2	1400 (2)	1310	10 (2)	8		
		4/27/50	1.0	3	+0.5 (3)	-2	1453 (3)	1773	8 (3)	49		
		5/5/50	1.0	3	-2 (3)	-2	880 (3)	1522	3 (3)	58	1.7	
20	C.M., W. M., 52 HCVD	9/18/50	1.0	5	-3 (5)	-7	1500 (4)	2814	20 (4)	143	2.7	
						Renal Disease						
21	F.M., W. F., 48 Kimmelstiehl-Wilson	11/16/49	1.2	1			1223 (2)	1830	53 (2)	123	2	Uremia
22	M.B., C. F., 32 Nephrotic syndrome	1/22/50	1.2	3	-1.5 (3)	-13.5	797 (3)	2733	40 (3)	241		Normal renal function
		2/1/50	1.2	3	-2.5 (3)	-8.5	1533 (3)	2982	50 (3)	185		
		2/10/50	1.2	3	+0.5 (3)	-2.5	1870 (3)	2430	23 (3)	61	3.3	
23	C.C., C. F., 39 Hypertensive nephrosclerosis	2/12/50	1.0	1	-2 (1)	-3	540 (1)	1240	13 (1)	32		Thoracentesis while on drug; uremia
		2/24/50	1.2	3	+1.5 (3)	+.5	843 (3)	833	26 (3)	39	1	
24	H.D., W. M., 50 Nephrotic syndrome	2/20/50	1.0	1	-2.5 (1)	-3	2660 (1)	3490	126 (1)	280		Anorexia; normal renal function
		6/28/50	1.0	2	-4.5 (2)	-3.5	1865 (2)	2520	126 (2)	235		
		7/11/50	1.0	3	-1 (3)	+.5	1060 (3)	1787	0.6 (3)	2	2.3	
25	C.H., W. F., 52 Kimmelstiehl-Wilson disease	2/19/50	1.25	4	+1 (1)	-8	370 (1)	762	1 (1)	35		Uremia; nausea; no vomiting
		2/25/50	1.25	2	-.5 (2)	+1	395 (2)	700	4 (2)	6	1.3	
26	M.W., C. F., 22 Nephrotic syndrome	2/28/50	1	3	-1.5 (3)	+1.5	227 (3)	648	5 (3)	15		Renal function good
		3/9/50	1	3	+1.5 (3)	+.5	1860 (3)	1753	3 (3)	3		
		5/19/50	1.25	4	+1 (3)	+1	650 (2)	842	3 (2)	6	0	
27	A.D., W. F., 63 Chronic nephritis	5/5/50	1.0	2	0 (2)	0	136 (2)	139	0.7 (2)	0.8	0	Terminal uremia
28	V.S., W. M., 51 Kimmelstiehl-Wilson disease	5/26/50	1.0	2	+1 (2)	-.5	2360 (1)	2725	64 (1)	122	1	Vomiting; uremia

TABLE II (Continued)

Case No.	Patient, Race, Sex Age, Diagnosis	Date Drug Course Started	Dose gm./day	Duration of Drug Course (days)	Weight Change, Control Period (lb.)	Weight Change, Drug Period (lb.)	Urine Volume, Control Period (cc./day)	Urine Volume Drug Period (cc./day)	Na Excretion Control Period (mEq./day)	Na Excretion Drug Period (mEq./day)	Diuretic Response Index	Remarks
29	F.W., W. M., 31 Nephrotic syndrome	9/30/50	1.0	3	0 (1)	-7.5	1900 (1)	2967	89 (1)	161	2.3	
30	A.J., W. M., 38	11/12/50	1.2	1	0 (1)	0	500 (1)	435	1 (1)	29		
	Chronic glomerulo-nephritis	3/8/51	1	5	+1 (5)	-11	835 (2)	1444	6 (2)	22		Uremia
		3/20/51	1	8	0 (7)	+.5 (8)	606 (7)	709	7 (7)	6	2	
31	A. M., W. M., 20 Nephrotic syndrome	2/15/51	1.25	4	+.5 (3)	-9	1400 (3)	2710 (3)	54 (3)	196		In hospital-anorexia; impaired renal function
		2/20/51	1.0	5	-.5 (1)	-7.5	1800 (1)	2560 (1)	92 (1)	152		
		3/6/51	1.0	7	+22.5 (8)	-6						Anorexia
		3/13/51	1.0	7		-3	on drug 3088 this period					No anorexia — Outpatient
		3/20/51	1.0	7		-1					2.7	Anorexia
32	W.F., W. M., 46 Kimmelstiehl-Wilson Disease	3/7/51	1.0	4	-4 (4)	-9	1690 (4)	1937	75 (4)	106	1.3	Uremia
						Cirrhosis						
33	L.J., C. M., 39 Cirrhosis of liver	1/15/50	1	3	-.5 (3)	-5	3770 (3)	3513	132 (3)	114	0	Weight loss suggests inaccurate urine collection
34	R.D., W. F., 46 Cirrhosis of liver	2/22/50	1.0	3	+2 (2)	-18	673 (2)	3612	29 (2)	393	4	
35	A.L., W. M., 41 Cirrhosis of liver	5/10/50	1.2	5	+7 (5)	-1					0	Urine not collected
36	P.P., W. M., 71 Cirrhosis of liver	5/14/50	1.0	3	0 (3)	-14						Previous thiomerin 2 cc.; S.C. -4 lb. weight loss
		6/12/50	1.0	3	0 (3)	-14						
		7/15/50	1.0	3	0 (3)	-4					3	Nausea, no vomiting
37	T.I., W. M., 56 Cirrhosis of liver	5/26/50	1.0	3	-1.5 (3)	0						
		6/6/50	1.0	3	+4 (2)	+3					0	

*Number in parentheses in control columns indicates number of days control observations.
Weight change for control period is total weight change during control period.
Urine volume and sodium excretion during control period are average daily excretions for the number of control days indicated in parentheses.
Weight change on drug is the total weight change during the period of drug administration.
Urine volume and sodium excretion while on drug are represented as the average daily excretion for the period of drug administration.
HCVD = Hypertensive cardiovascular disease
ASHD = Arteriosclerotic heart disease
RHD = Rheumatic heart disease

have attempted to derive an index of diuretic response for each patient in the following manner: With respect to weight, a loss of less than 2 pounds during the course of drug therapy was scored 0, loss of 2 to 5 pounds was scored 1, loss of 5 to 10 pounds scored 2, loss of 10 to 15 pounds scored 3 and loss of more than 15 pounds scored 4. With respect to urine volume an average daily increase while on the drug of less than 200 cc. scored 0, 200 to 500 cc. scored 1, 500 to 1,000 cc. scored 2, 1,000 to 2,000 cc. scored 3 and over 2,000 cc. scored 4. With respect to sodium excretion an average daily increase while on the drug of less than 25 mEq. scored 0, 25 to 50 mEq. scored 1, 50 to 100 mEq. scored 2, 100 to 150 mEq. scored 3 and over 150 mEq. scored 4.

TABLE III

Diuretic Response Index	0	1	2	3	4
No. of Patients with:					
Congestive failure	5	3	7	5	
Renal disease	2	4	4	2	
Cirrhosis	3		1		1
Total	10	7	12	7	1

In each patient the period of best performance for each of these measurements was scored. The scores were then added together and divided by three thus yielding a figure lying somewhere between 0 and 4, and conforming roughly to a 1+, 2+, 3+ and 4+ response. For example, patient No. 1 in his first test period scored 1 on the weight measurement, 4 with respect to increase in urine volume and 4 with respect to increase in sodium excretion for a total score of 9 of a possible 12. Since three measurements were made, the 9 is divided by 3 to give a diuretic response index of 3, a very good response indeed. In summarizing the results the fractional indices have been rounded off to the nearest integer. Only those thirty-seven patients observed in the hospital have been used for this estimation of the drug's effectiveness.

RESULTS

Table III shows the distribution of patients in the three clinical groups according to their diuretic response indices.

Since an index of 1 represents an appreciable diuretic response and indices of 2 and above represent excellent to extraordinary responses, we feel justified to say that the drug had a definite effect in 73 per cent of the thirty-seven patients employed in the analysis. In 27 per cent there was no response.

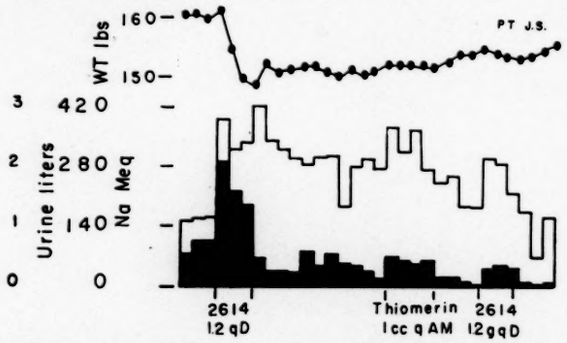


FIG. 3. Effect of 2614 in patient No. 13, a white male, age sixty-seven, with congestive cardiac failure due to arteriosclerotic heart disease. Daily urine volume can be seen from base line to top of clear area. Daily sodium excretion is shown in black; there was marked diuretic response to 2614 and small responses subsequently to thiomerin and 2614.

Patients with Cardiac Failure. Figures 3, 4, and 5 illustrate examples of satisfactory diuretic responses in cases of congestive cardic failure. These charts emphasize two important points. First, the marked augmentation of sodium excretion and urine volume with concomitant loss of weight associated with administration of the drug is clearly shown. Secondly, it will be seen that one cannot compare the diuretic effect of 2614 with mercurial diuretics in the same patient at different times because the responsiveness of a patient to diuretic agents is constantly changing during the course of the illness. For example, Figure 3 shows a patient who had a good diuretic response to the first course of 2614 bringing him promptly to his dry weight. A subsequent four-day course of thiomerin brought about only a small response while still another course of 2614 resulted in only a small response.

A similar phenomenon is exhibited by patient G. C. in Figure 4, who showed only a moderate response to the first day of 2614 therapy. On the third day the patient received both 2614 and thiomerin with a good result but the next two days on thiomerin alone resulted in only fair diuresis. After a three-day rest 2614 brought about a good sustained diuresis, but subsequent courses of 2614 and thiomerin caused only small responses. It ap-

pears that the diuretic responsiveness of these patients bears some relationship to their edematous state. When they lost their edema, they showed only meager responses to diuretic drugs in contrast to the non-edematous subjects, most of whom exhibited large sodium and water chronic glomerulonephritis. The response of patient 22 to therapy is illustrated in Figure 6. Two separate courses of 2614 resulted in striking sodium and water diuresis. A third course given when patient still had slight clinical edema resulted in only a slight diuresis. Patient

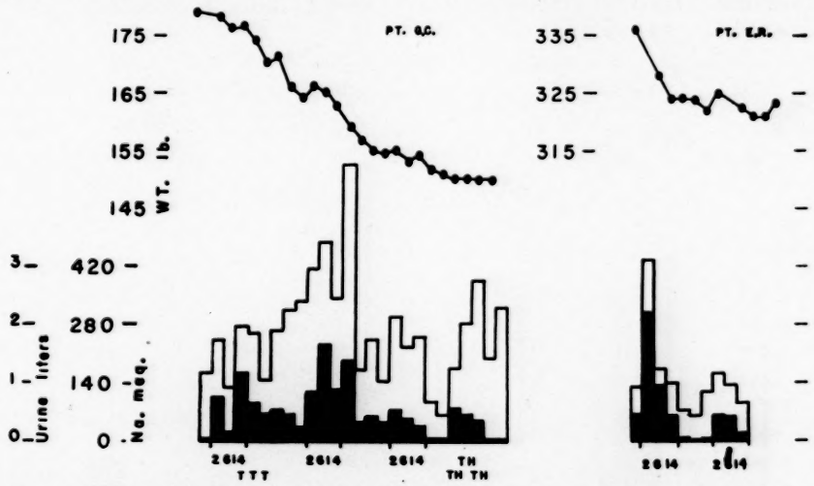


FIG. 4. Effect of 2614 and thiomerin in patient No. 11, a colored male age forty-eight, in congestive failure due to arteriosclerotic heart disease. Thiomerin (2 cc.) was subcutaneously administered on days marked T and TH. A second course of 2614 produced diuresis exceeding first course of 2614 and thiomerin. Subsequent courses produced small diuretic response. Also shown is response of patient No. 7, a colored male, age forty-seven, in congestive failure due to hypertensive cardiovascular disease and obesity. Large diuresis occurred with first course of 2614 and only a small response to second course.

diuresis with administration of 2614 or mercurial. This difference is probably related to the fact that all the cardiac patients were on low salt diets although the normals were consuming normal quantities of salt.

Five of the cardiac patients failed to respond to 2614. Three of these (patients 6, 8, 9) also failed to respond to mercurials. Patient 9 had a low serum sodium concentration of 133 to 118 mEq./L. When this concentration was subsequently elevated by increasing dietary salt and restricting fluids, responsiveness to thiomerin was restored. This phenomenon was observed by Keith and Whelan[4] in 1926. Patients 3 and 18 subsequently had excellent responses to mercurials. Patient 17 who responded to 2614 with an index of only 1 later responded to mercurials with an index of 4. On the other hand, patient 15 who had a good response to 2614 showed no response whatever to a mercurial.

Patients with Renal Disease. Four of the patients with primary renal disease who were tested on 2614 had the nephrotic stage of 31 failed to respond to a trial course of 2614 at a time when he was massively edematous. It was not until approximately 80 pounds of edema fluid had been drained off through Southey tubes and about 20 pounds had subsequently reaccumulated that he showed a striking diuresis on drug therapy.

Patient 24 was already undergoing spontaneous diuresis when 2614 was given. There was, however, very marked augmentation of this diuresis during drug therapy. Patient 26 showed no response at all. Three nephrotic children of ages three, four and five were given the drug in doses of 125 mg. two or three times a day while being observed as outpatients. None of these showed any improvement or diuretic response.

Five patients exhibiting the Kimmelstiehl-Wilson type of diabetic nephrosis were treated with 2614, and all of these showed fair to moderate responses to the drug despite the presence of marked renal insufficiency in each of them.

One patient in the late stages of chronic

glomerulonephritis had a fair response while another in a terminal condition failed to respond.

One patient in uremia due to hypertensive nephrosclerosis responded slightly.

Patients with Cirrhosis of the Liver. Two of five patients with ascites and edema due to cirrhosis of the liver had excellent responses to

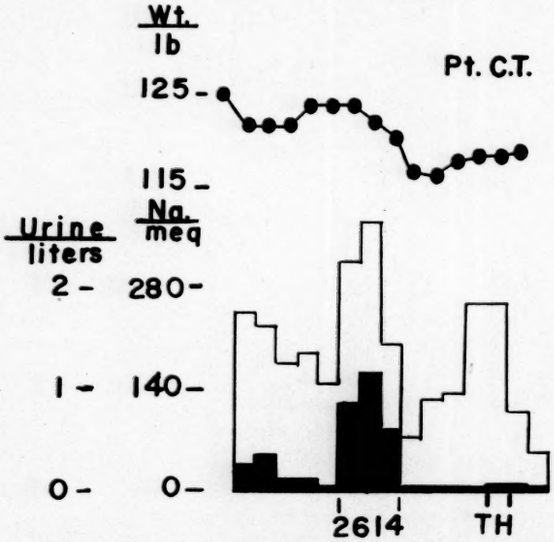


FIG. 5. Effect of 2614 and thiomerin in patient No. 15, a colored male, age sixty-eight, in congestive failure due to chronic cor pulmonale secondary to emphysema. Administration of 2614 produced good diuresis. A subsequent dose of thiomerin 2 cc. subcutaneously produced no response. Later when edema had reaccumulated, the patient showed good response to thiomerin.

2614. One of these, as shown in Figure 7, had the only maximal index of diuretic response seen in the whole series. This patient happened to be the only female cirrhotic treated. It was unfortunately impossible to collect urine from three of the five patients so that the index had to be based on the weight loss alone.

Outpatients. Data are also available on a series of patients treated in the outpatient department. In these the only available information relates to change in weight. Patient 41 in this group showed the most striking response with 6 to 7 pound weight gain during seven-day periods off the drug and 7 to 8 pound weight loss during seven-day periods on the drug in the usual doses. Patient 40, while not showing marked weight loss, had striking relief of pain due to a very large tense liver, this organ diminishing strikingly in size during three days on the drug. Patient 44 could not be maintained at dry weight with either 2614 or thiomerin alone but on a combination of the two was well controlled. After several weeks lapse of therapy she was admitted to another hospital where 20 pounds of edema were removed in a seven-day course of 2614.

In this group two cardiac, three juvenile nephrotic and one terminal glomerulonephritic patients failed to respond.

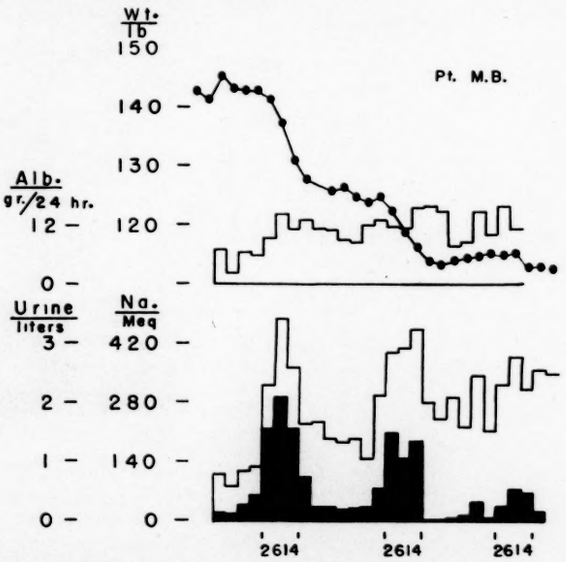


FIG. 6. Effect of 2614 in patient No. 22, a colored female, age thirty-two, in the nephrotic stage of chronic glomerulonephritis. There were two marked diuretic responses to administration of 2614; one lesser response when slight edema was still present. Urinary albumin determined by McKay's method employing Tsuchyia's reagent showed a tendency to increase slightly with larger urine volume.

Toxicity. Of the fifty patients who have been treated with 2614, thirteen or 26 per cent have had gastrointestinal complaints. Three of these voluntarily complained of anorexia. Five complained of nausea without vomiting while five had vomiting and one had diarrhea in addition to vomiting. On close questioning a number of the other patients did admit to mild sensations of gastric discomfort but did not complain about it. One patient, No. 31, who has had continuous administration of the drug for six weeks had anorexia during the first two weeks but has had none since.

No evidence of renal damage has been detected. All patients have had urinalyses before, after and many of them during treatment. Despite the fact that some of the patients had active renal disease no alterations in the urinalyses were found. Two of the nephrotic patients, No. 22 and 24, had Addis counts before, during and after treatment. There was no significant

difference between any of these. Albumin excretion determined during control periods and during drug therapy increased slightly with drug administration but appeared to be more closely related to the urine volume than to

Urinalyses and phenolsulfonphthalein tests done on each patient before and after each test showed no alterations.

Three patients have been given therapeutic courses of 3088 while being followed up in the outpatient department. Two of these, patients 31 and 41, appeared to have slight diuretic responses. The other, patient 30, had no response although his chronic glomerulonephritis was approaching its terminal phase.

TABLE IV

EFFECT OF 3088 IN FIVE NORMAL SUBJECTS

Drug Dose gm./day	Drug Day Urine Volume % of Control	Drug Day Na Excretion % of Control	Drug Day K Excretion % of Control	Urine Volume Follow-up Day % of Control	Na Excretion Follow-up Day % of Control	K Excretion Follow-up Day % of Control
1	183	194	117	86	71	94
2	174	171	131	69	64	83

administration of the drug. No effect on phenolsulfonphthalein excretion was noted in any case.

So far no instances of skin rash, fever or alterations in hemoglobin or leukocytes have been encountered. The patients with cirrhosis showed no evidence of worsening of the liver disease.

OBSERVATIONS ON 1-ALLYL-3-ETHYL-6-AMINOURACIL

This compound was tested in the hope that it might have less gastrointestinal effect than 2614. Five normal subjects were given compound 1-allyl-3-ethyl-6-aminouracil, which has the serial number 3088, in doses of 250 mg. four times in one day following three days of control observation. Observation was continued during one recovery day. Control data were averaged for urine volume, sodium excretion and potassium excretion in each subject and these values on the test day are shown as per cent of the averaged control. This figure for all five subjects was averaged and is shown in the top line of Table IV. A similar average is shown for the recovery day.

It will be seen that compound 3088 has an effect in normal subjects almost identical to that of 2614. There were no gastrointestinal complaints during this test. One month later, a similar test was carried out on the same subjects this time with double the dose of 3088 or 500 mg. four times in one day. The response was less than that seen with the lower dose. This observation is similar to that seen with 2614, the lower dose having a greater effect.

This second test with the 2 gm. dose of 3088 caused nausea in four of the five subjects. One subject vomited. One subject had no symptoms.

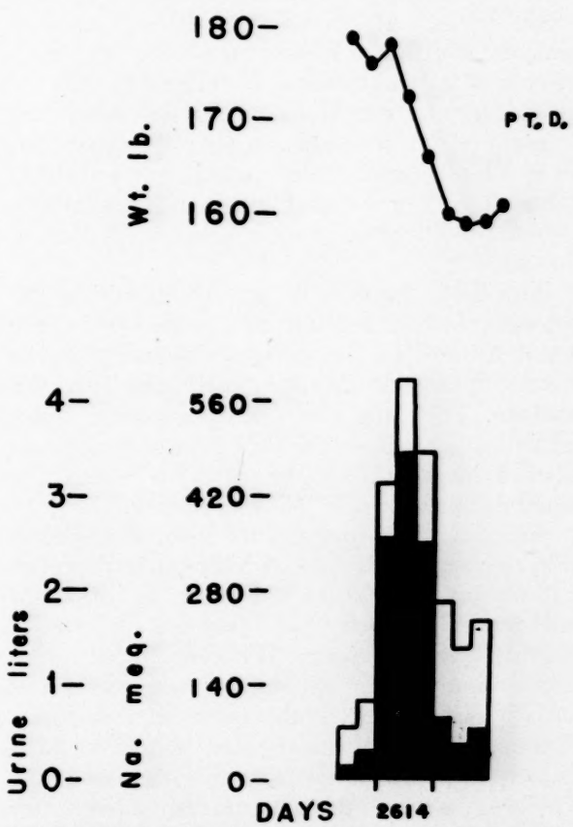


FIG. 7. Effect of 2614 in patient No. 34, a white female, age forty-six, with ascites and ankle edema due to cirrhosis of the liver. This was the most striking diuretic effect in the entire series.

Patient 31 had had anorexia on 2614 but regained good appetite on 3088. Later anorexia disappeared while on continuous administration of 2614. Patient 41 who complained of mild nausea on 2614 had worse nausea on 3088 and vomited once during a seven-day course of drug therapy.

Patient 30 was given 3088, 1 gm. every day for five days, with no loss of weight. There were no gastrointestinal symptoms with either 2614 or 3088.

It is our impression from these preliminary observations that the diuretic potency of 3088 is about the same as that of 2614, and that 3088 causes about the same degree of gastrointestinal irritation as 2614.

COMMENTS

The clinical experience to date with drug 2614 seems to indicate that it has definite diuretic potency and that it is quite non-toxic. The side-effects of gastrointestinal disturbances may be minimized by employing doses not exceeding 1 gm. per day in adult patients. The fact that it is administered orally constitutes a distinct advantage over existing diuretic preparations. Active renal disease is not a contraindication to its use.

The drug appears to act by inhibiting the reabsorption of sodium and chloride in the renal tubule. In the normal controls chloride excretion in each instance closely paralleled the sodium. The drug also seems to have a lesser effect on potassium, the excretion of which was always increased by the drug to about the same extent shown in Tables I and IV.

An exact comparison of the therapeutic effectiveness of this drug with mercurial diuretics cannot be made from our data. In the non-edematous subjects 2614 seemed to be of slightly greater potency. However, in the edematous patients it appeared that mercurials usually had a greater and more reliable effect. Some patients who responded poorly to 2614 subsequently had large diureses with mercurials. However, a few of the patients responded better to 2614 than they did to mercurials. More study will be required before such a comparison can be validly established.

SUMMARY

1. Clinical trials of a new oral diuretic compound, 1-propyl-3-ethyl-6-aminouracil, are described.

2. This compound was non-toxic to dogs in double the human dose administered continuously for ten days.

3. In ten normal subjects one day's administration of the drug produced a sodium and water diuresis equal to that produced by a mercurial diuretic.

4. Thirty-seven hospital patients with edema due to cardiac failure, renal disease or cirrhosis of the liver have been treated with the drug. A definite diuretic effect was produced in 73 per cent of these; 54 per cent had excellent therapeutic benefit. Thirteen outpatients have also been treated.

5. No serious toxic manifestations have been noted although 6 per cent of patients have complained of anorexia, 10 per cent have had nausea without vomiting, 8 per cent have had vomiting and one patient or 2 per cent has had vomiting and diarrhea.

6. The mode of action of the drug appears to be a specific inhibition of sodium and chloride reabsorption in the renal tubule.

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Review

Electrokymography*

I. The Ventricular Electrokymogram

SIMON DACK, M.D. *and* DAVID H. PALEY, M.D.
New York, New York

ELECTROKYMOGRAPHY,[1–4] a comparatively new method for the study of cardiac pulsations, is based on the use of the multiplier type phototube, the application of which was first suggested by Morgan.[5] The technical details of the method have been fully described elsewhere.[1–5] Briefly, the photosensitive tube, which is attached to the fluoroscopic screen, contains a rectangular slit covered by a small fluorescent screen. When the tube is adjusted so that the slit is placed over the cardiac border during fluoroscopy, the cyclic variations in light produced by the movement of the underlying cardiac border result in a pulsating flow of electrons which is amplified and recorded by a galvanometer in the form of a phasic curve.

The kymographic curve obtained by this method is a result of volume and positional changes in the heart during contraction and filling. The volume changes produce inward and outward movement of the cardiac border and variations in density of the underlying chamber. The positional changes are due to displacement, torsion and change in contour of the heart during systole and diastole. Upward movement of the curve represents outward or lateral movement of the cardiac border or increased density of the underlying chamber. Downward movement of the curve represents inward or mesial motion of the border or decreased density.

By placing the fluorescent slit of the phototube over the various segments of the cardiac borders in the posteroanterior and both oblique positions a distinctive electrokymogram from the four cardiac chambers and from the great vessels can generally be recorded in the majority of individuals. In this review we shall describe the normal variations of the left ventricular kymogram and the changes produced by myocardial disease. In a subsequent review we shall deal with electrokymograms of the auricles and great vessels and their applications.

NORMAL VENTRICULAR CURVES

The study of left ventricular border motion has added to our knowledge of the physiology of normal ventricular contraction and has aided in the detection of abnormal contraction in myocardial disease. It has been particularly useful in myocardial infarction in which abnormal contraction has been detected when other methods have failed to disclose the infarction or have confirmed the findings at a later date.[6] Our method[6,7] which utilizes simultaneous recording of the heart sounds, carotid pulse tracing and electrocardiogram with the electrokymogram lends itself admirably to detailed analysis of the various phases of the ventricular curve in systole and diastole.

With minor variations kymographic curves obtained along the left ventricular borders are closely similar. They resemble a ventricular volumetric curve upon which are superimposed positional movements which occur at the onset of systole and diastole. In general, a typical ventricular curve (Figs. 1 to 4) consists of a steep rapid downward movement due to inward motion of the ventricular wall during ventricular ejection and a less steep upward movement due to outward motion during ventricular filling. The downward movement during ejection is preceded by a short shallow segment which may be directed horizontally, upward or downward in the isometric phase of systole. Very often the onset of the ejection phase also shows a short upward or horizontal segment which precedes the steep downward movement. This segment generally lasts for 0.02 to 0.04 second and

* From the Cardiovascular Research Group and the Cardiographic Laboratory, The Mount Sinai Hospital, New York, N. Y.

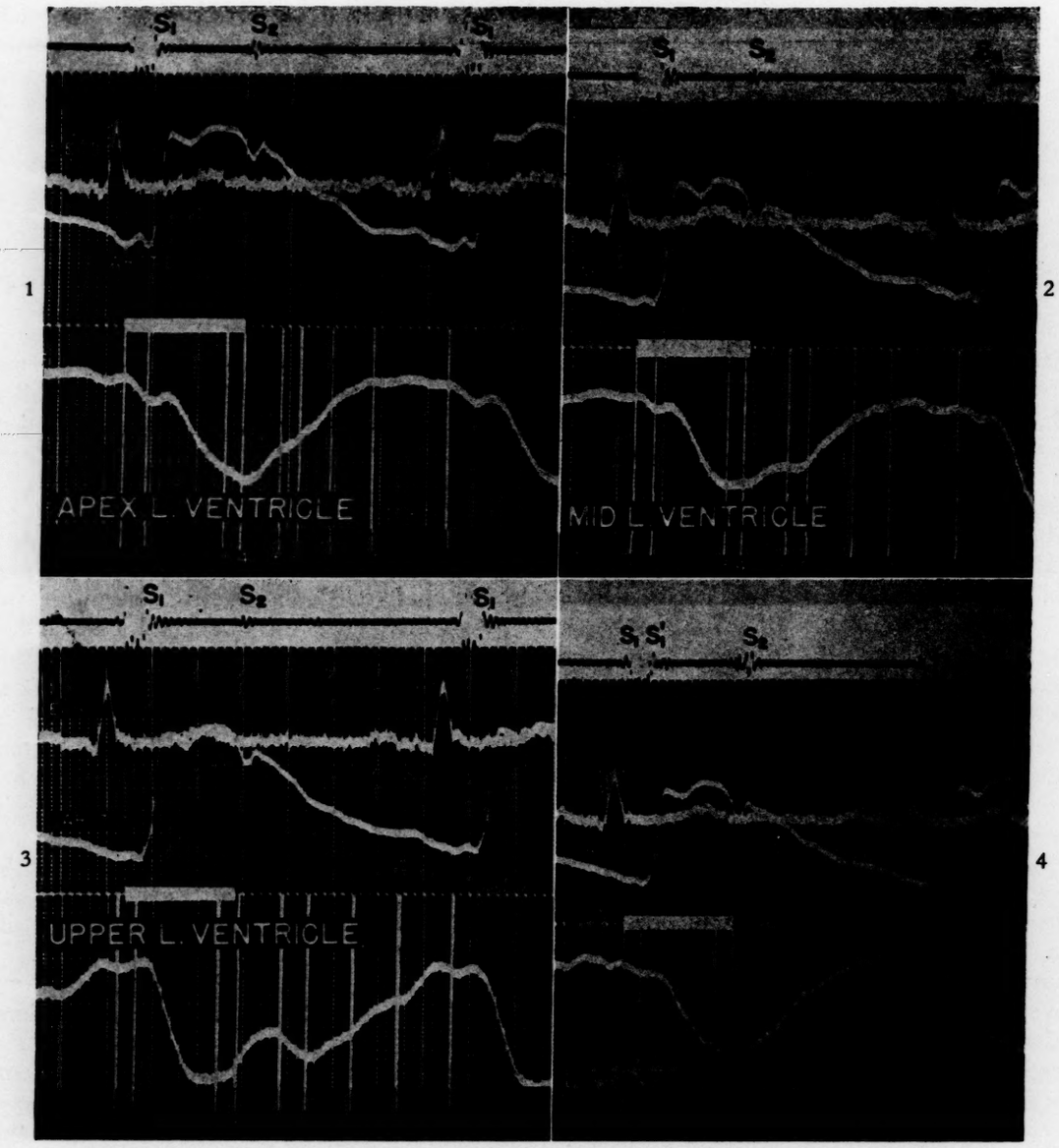


FIG. 1. Ventricular electrokymogram of normal subject obtained from border of apex of left ventricle and recorded simultaneously with phonocardiogram, electrocardiogram and carotid pulse curve. Vertical time lines equal 0.02 second. Phase 1 to 2, isometric contraction; 2 to 3, ejection; 3 to 4 protodiastole; 4 to 5 isometric relaxation; 4 to 5′ alternative limits of isometric relaxation phase; 5 to 6 rapid filling; 6 to 7 slow filling; 7 to 1, diastasis and ventricular filling during auricular contraction. Note that in following figures of same subject there are minor variations in duration and configuration of these phases due to differences in positional movement.

FIG. 2. Normal ventricular electrokymogram of same subject as in Figure 1 obtained from mid-left ventricular border. Phase lines 1 to 7 same as in Figure 1.

FIG. 3. Normal ventricular electrokymogram of same subject as in Figure 1 obtained from upper left ventricular border. Note characteristic form of isometric relaxation phase (4–5′); segment 4–5 is considered by some to constitute entire phase, while 5–5′ is considered rebound of ventricle during early filling phase. Other investigators consider segment 5–5′ part of isometric relaxation phase.

FIG. 4. Normal ventricular electrokymogram of same subject as in Figure 1 obtained from lower left ventricular border in slight left oblique view.

occasionally for 0.06 second. It is not to be considered abnormal unless the duration exceeds 0.06 or 0.08 second. Similarly, the outward movement of the ventricle during filling is preceded by a short segment directed upward or downward which occurs during the isometric relaxation phase and is not properly a part of the ventricular filling phase. Generally, the right ventricular electrokymogram is similar to the one obtained for the left ventricle but is often distorted by superimposed movements of the juxtaposed right auricle.

The appearance and timing of the segments of the ventricular curve undergo variations as one moves the kymographic head downward along the left ventricular border. Since the ventricular muscle does not contract as a unit simultaneously but in a wave-like fashion, one might logically expect that the muscle first activated is first to contract; thus one finds earliest movement at the apex and delayed movement at the base. The base is drawn toward the apex, which is displaced slightly in an upward direction, so that the heart is shortened in its longitudinal axis. At the same time there is rotation to the right, so that the positional change of anterior displacement of the left ventricle is registered in the tracing. These positional changes, however, may so modify the curve that a regular sequence of contraction may not be readily discernible.

The Isometric Contraction Phase. During this period of the cardiac cycle the ventricles are closed chambers contracting against a constant volume of blood. In the left ventricle it is initiated by closure of the mitral valve and terminated by opening of the aortic valve. It is evident that any movement of the electrokymographic curve during this period can reflect only a positional change of the heart consequent to the onset of ventricular contraction and not a volumetric change. Since abnormal ventricular movement produced by myocardial disease often begins in this segment or may be restricted to it and since this phase may be prolonged in myocardial disease, its accurate analysis and measurement is of more than academic importance. This, however, is not an easy task since the reference points required for the determination of its onset and termination are often indistinct.

Scandinavian and French workers utilized the electrocardiogram.[8,9] The peak of R or the mid-point of its downstroke was considered the point of onset of the isometric contraction phase. This is an arbitrary method subject to error since there may be considerable variation in the sequence of electrical activation and mechanical response of the myocardium in different individuals and in cardiac disease. Furthermore, the end of the isometric contraction phase cannot be determined from the electrocardiogram. Luisada and his co-workers[4,10] and others[11] have employed the phonocardiogram as the reference tracing. By this method it is considered that isometric contraction begins with the initial major vibrations of the first heart sound (A-V valve closure) and ends with the beginning of the second component of the first heart sound (opening of the semi-lunar valves). From a technical point of view this method is objectionable because good heart sound tracings are often unobtainable in the sitting posture and chest noises and other extraneous sounds may introduce artifacts that render end points speculative. More important, perhaps, is the fact that asynchronism of the onset of left and right ventricular contraction may exist normally, the duration of which may vary from 0.01 to 0.03 second. The initial vibrations of the first heart sound, therefore, are produced by the leading ventricle which, peculiarly enough, is more often the right than the left. Many workers, notably Chamberlain, Henny and Boone,[1–3] have used the carotid pulse tracing as the timing device for this period. With corrections for lag this method is very well suited for ascertaining the end of the isometric period but is inadequate for determination of the onset.

We[6,7] have utilized all of these methods simultaneously; and although the objections to the methods apply here also, we believe that the margin of error is less because of their combined use. The onset of the isometric phase is determined from the initial vibrations of the first heart sound after suitable precautions are taken to exclude the low-pitched vibrations of the auricular sound. When the right ventricle contracts first (as can easily be determined by the relationship of the rise of the pulmonary artery kymogram to that of the carotid pulse), the necessary corrections are made. The end of the period is determined from the sharp rise of the carotid pulse after correction is made by deducting the lag through the recording apparatus and the time of conduction of the pulse wave to the carotid artery. This generally amounts to not more than 0.02 second. If the

second component of the first heart sound is present as a sharp, well defined vibration, it serves as a useful check on the accuracy of the carotid pulse curve.

In ventricular curves obtained from normal individuals the form of this phase is subject to considerable variation depending on many factors such as the point of the left ventricular border from which the curve is obtained and the habitus and position of the patient. It may be represented by upward, horizontal or downward movement. (Phase 1–2, Figs. 1 to 4.) Moreover, it may be shallow or steep in either direction. At the base (Fig. 3) it is often recorded as a steep upward movement almost continuous with the upward movement of the preceding diastolic curve. In curves obtained near the apex (Fig. 1) this phase usually appears as a downward directed segment while a horizontal segment may be obtained in the middle portions of the left ventricle. These differences, however, are extremely labile and any form may be found at any location because the border motion during this phase of the ventricular kymographic curve is due to purely positional changes in the heart.

There is generally good agreement concerning the duration of this phase for the left ventricle, the average duration being about 0.04 second. Almost all workers have found the upper limit to be 0.06 second. Even Willis and co-workers[11] who observed durations as high as 0.08 second concede that this figure is probably erroneous and due to asynchronism of the ventricles. The isometric contraction phase of the right ventricle has been reported to be somewhat shorter than that of the left ventricle. Our observations have confirmed this finding. We have found it to range between 0.02 and 0.05 second. This may be partly responsible for the slight ventricular asynchronism in normal individuals in whom right ventricular ejection may lead the left by 0.01 to 0.03 second. In contradistinction to the variations in form this phase is remarkably constant in duration in the healthy heart, neither rate, positional changes or any other factor apparently having any influence.

Wiggers[12] found that there was a tendency to lengthening of the duration of this phase in the left ventricle when the abdominal aorta was clamped, a prolongation which he attributed to the increased peripheral resistance. In essential hypertension, however, in which peripheral resistance is increased we have found no significant alterations in the duration of this period. This contrasts sharply with the observed effects of hypertension on the isometric relaxation period. Prolongation of the isometric contraction period has been reported in aortic and pulmonic stenosis in which there may be delay in opening of the stenotic semi-lunar valves.

Ejection Phase of Systole. This phase is characterized by predominant downward movement, usually rapid and deep, representing mesial systolic movement of the ventricle. (Phase 2–3, Figs. 1 to 4.) The onset of downward movement, however, may be preceded by a short upward wave which is caused by a positional change of the heart occasioned by traction of the filling aorta, pendulum and spiral motion of the heart, and change in shape of the heart.[3] This positional change produces movement of the heart border in a direction which may neutralize or reverse the inward movement expected to occur at this time. The onset of the short upward movement generally coincides with the second component of the first heart sound (which represents the opening of the semilunar valves) and the initial upstroke of the carotid pulse curve. (Fig. 4.) This component of the ejection phase may be continuous with the isometric phase if the latter is represented by upward movement. In other words the positional changes responsible for outward movement of the ventricular border generally begin in the isometric phase and may continue into the early ejection phase. In our experience and in that of others[13] this positional effect is less pronounced as the kymographic head is moved from the base toward the apex of the left ventricle but the opposite variation has been observed. (Fig. 3.) Although exact measurements are difficult and frequent variations occur, it is generally agreed that the duration of this upward segment, like that of the isometric phase of systole which precedes it, does not exceed 0.06 second. Beyond this point upward movement during the ejection phase is considered by us to be paradoxic or a reversal of pulsation and indicative of myocardial weakness.[6]

The duration of the downward movement of the ejection phase varies slightly with the heart rate but in our experience it averages about 0.2 second. Downward movement in the ventricular curve usually terminates before the onset of the second heart sound and dicrotic notch of the carotid pulse curve (Fig. 3) but considerable variation may occur even in the same heart

when several segments are compared. We have noted that the downward movement of ejection may terminate synchronously with the latter two events (Fig. 1) or may even be prolonged beyond them. Willis and co-workers[11] found that the duration of the ejection phase as determined from measurements of the aortic knob kymogram showed wide variations in normals, both in the rapid and reduced phases. In a series of sixty normal individuals they found a range of 0.17 to 0.32 second for total ejection, with a mean duration of 0.23 second. This was in fairly good agreement with the early figures of Katz and Feil[14] (0.22 to 0.28 second). Moreover, they found that in longer cycle lengths the reduced phase of systolic ejection showed a tendency to lengthen in duration while the rapid phase did not.

Protodiastolic Phase. This phase is the interval between the termination of ejection and closure of the semi-lunar valves. It is therefore actually a part of systole. It has a remarkably constant duration of about 0.04 second in normal subjects, almost all investigators agreeing on this figure. On the electrokymographic curve it is often seen as a more shallow downward movement, continuing from the end of the ejection phase as a slightly angular departure and terminating rather sharply in the isometric relaxation phase. (Phase 3–4, Fig. 1.) Its nadir may coincide exactly with the carotid incisura when the necessary corrections for lag are taken into consideration. Little is known about alterations in this phase of the cardiac cycle.

Isometric Relaxation Phase. This phase, in which the ventricle is a closed chamber, lies between the end of protodiastole (closure of semi-lunar valves) and the beginning of ventricular filling (opening of A-V valves). Boone and co-workers[15] believed that this phase is represented in the electrokymogram by an easily identifiable segment, namely, an inverted V-shaped movement. (Phase 4–5, Fig. 3.) The end of the descending limb was considered the end of isometric relaxation. Luisada and co-workers,[16] however, believe that when such a typical curve is present the peak of the V marks the end of isometric relaxation (Phase 4–5) and the descending limb is the onset of ventricular filling. Our own experience has been that such a V-shaped curve is often absent and that it may be represented by a horizontal segment or a short upward movement. (Figs. 1 and 4.) When a V-shaped curve is present (Fig. 3), our measurements appear to support Luisada's contention. Since there is no volumetric change in the ventricles during this phase, the recorded movements are entirely positional in nature and like those observed during isometric contraction are subject to considerable variation in form. We are in perfect agreement with Akman and co-workers[13] who also emphasized the variability of this phase in normal individuals.

The isometric relaxation phase has attracted the attention of many physiologists who thought that its duration depended to a great extent on the functional condition of the myocardium. It is known[17] that during this phase there is a sharp rise in coronary blood volume flow so that a change in its duration might be important as regards myocardial nutrition. Its accurate measurement, however, has proven no easy task since the reference points for its measurement are subject to considerable error. The phonocardiogram would appear to be an excellent medium for this measurement, and in mitral stenosis, in which an opening click of the mitral valve may be clearly discernible, this method is ideal.[18] In normal subjects, however, the two components of the second heart sound are unfortunately seldom clearly delineated and this renders the phonocardiogram unsuitable in the majority of normal studies. Luisada and co-workers[16] analyzed the records of four normal patients in whom the mitral opening clock was clearly visible and found the isometric relaxation phase to range from 0.04 to 0.07 second with an average of 0.055 second. These figures are at considerable variance with those obtained by others using the electrokymogram.[11,15]

Boone and his co-workers[15] believed that the electrokymogram was an easy and accurate method for determining the duration of the isometric relaxation phase, first, because it produced in most cases the previously described characteristic curve and, second, because its accuracy was confirmed by superimposing recordings of the left atrial kymogram on the left ventricular kymogram, phonocardiogram and carotid pulse. The onset of the isometric relaxation phase was marked either by the incisura of the carotid pulse or the onset of the second heart sound, and the end of the period coincided with the onset of the V wave of the atrial kymogram. When the curves of 108 normal persons were analyzed in this way, they obtained values of from 0.06 to 0.16 second. Willis and co-workers,[11] utilizing essentially the

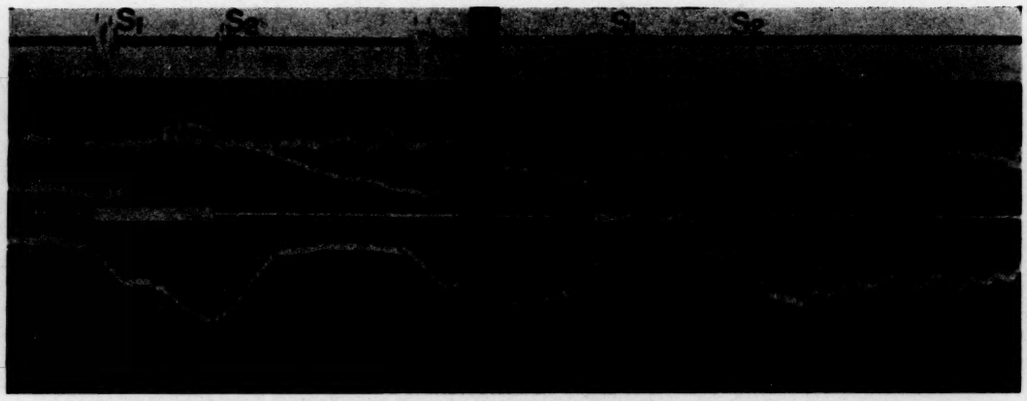


FIG. 5. Ventricular electrokymogram in myocardial infarction (complete reversal of pulsation). A, mid-left ventricular curve is fairly normal except for moderate diminution of amplitude during ejection. (Solid white horizontal bar represents entire systole.) B, curve of apex of left ventricle shows paradoxic pulsation with complete reversal of ventricular movement during systole. Collapse of the curve occurs at the end of isometric relaxation. The fibrillatory movements of the base line are due to the high magnification necessitated by the marked diminution of amplitude over the involved segment.

same method, obtained values of from 0.08 to 0.20 second (inclusive of the protodiastolic phase). Mednick, Schwedel and Samet,[19] using two phototubes and recording the atrial and ventricular curves simultaneously, obtained values of 0.07 to 0.14 second for the left ventricle and 0.10 to 0.13 second for the right ventricle.

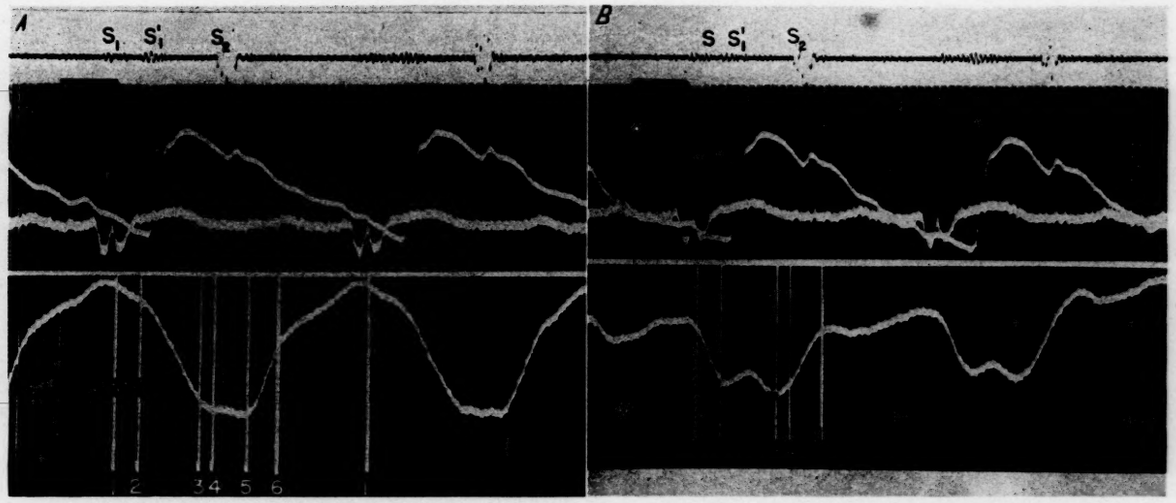
There is thus a fundamental difference in the normal values of this period obtained by different observers. It would appear that clear delineation of the two components of the second heart sound would be the most accurate method for obtaining the data. The electrokymographic method employed by Boone and others is open to criticism on the grounds that the electrokymogram, an instrument which is subject to some variation, delay and distortion due to factors inherent in the method and particularly to the influence of positional changes, is used as a check on the accuracy of the method itself. Moreover, the factor of asynchronism of the two ventricles is an operative source of error not only in the electrokymogram but also in the phonocardiogram. This controversy must be resolved before conclusions pertaining to variations in the duration of the isometric relaxation phase are considered. Using their own standards Boone and co-workers[15] and Lewis and Terry[20] observed an increased duration of this period in arterial hypertension and mitral stenosis. Further studies of this phase may contribute to our knowledge of impaired myocardial function in other diseases as well, but accurate figures in normal subjects must first be established. We will deal more exhaustively with this interesting phase of the cardiac cycle in a subsequent paper.[21]

VENTRICULAR CURVES IN MYOCARDIAL INFARCTION

Recording of the left ventricular electrokymogram has attained its greatest practical clinical value in the study and diagnosis of myocardial infarction.[6,7,22–25] The abnormalities of ventricular contraction may be visible during the systolic and diastolic phases of the cycle. The abnormalities of the systolic phase may be classified in three main groups: (1) localized diminution or absence of movement; (2) partial reversal of pulsation or transient outward ventricular movement during systole; (3) complete reversal of pulsation (paradoxic systolic pulsation) or sustained outward ventricular movement during the entire systole.

The abnormalities of the diastolic phase can also be classified in three groups: (1) mesial movement in early diastole; (2) retarded or absent filling; (3) complete reversal of pulsation or sustained inward movement throughout diastole.

Localized Diminution or Absence of Pulsation. In this abnormality of ventricular contraction the curve obtained over the involved segment shows marked diminution in amplitude during the ejection phase. (Fig. 5A.) The movements may be entirely absent, in which case ventricular ejection would be represented by a horizontal line or more likely by a series of small fibrillatory movements without particular slope, due to



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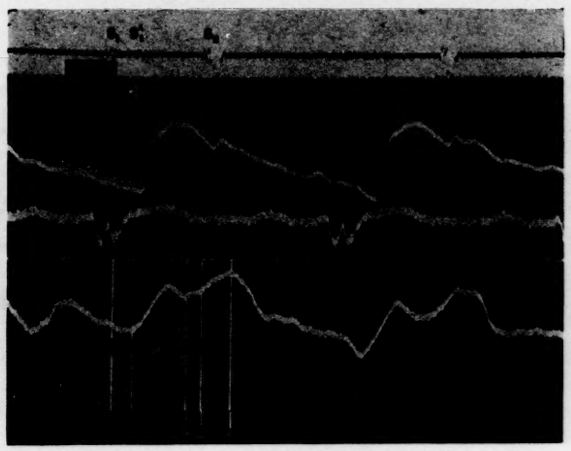

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FIG. 6. Ventricular electrokymogram in myocardial infarction (complete reversal of pulsation). A, upper left ventricular curve is normal. B, mid-left ventricular curve is abnormal. There is a sharp deep downward movement during isometric contraction (phase 1–2), markedly diminished movement during ejection (phase 2–3) and sharp upward movement during protodiastole and isometric relaxation (phase 3–5). C, lower left ventricular curve shows paradoxic movement with complete reversal of pulsation during systole. The paradoxic movement begins at the end of isometric contraction and continues throughout ejection (phase 2–3). There is a further rise of the curve during protodiastole which continues into isometric relaxation and early diastole and then diastolic collapse occurs.

artifacts produced by the high magnification required for recording. This type of curve probably results from impaired ventricular contraction which is not necessarily of such degree as to produce ballooning out of the involved segment during the rise of intraventricular pressure. We do not consider this abnormality to be pathognomonic of myocardial infarction but simply a manifestation of any type of localized muscle damage. It is often recorded in patients with large dilated hearts in the absence of infarction.

It must be remembered that to be significant of myocardial disease the diminished pulsation should be confined to a small segment of the left ventricular border and normal ventricular movement should be recorded at some point above or below this localized segment. Diminution or absence of pulsation in myocardial infarction has been observed most commonly over the lower or apical segment of the left ventricle.[26] In obese or sthenic individuals, however, care must be exercised when recording pulsations from the apical region where the ventricular movements normally may be somewhat diminished or obscured by the diaphragm or pericardial fat.

A variant of this abnormal type of curve which may occur in myocardial infarction is one in which a sharp mesial or downward movement occurs in the isometric phase of systole, followed by a horizontal segment indicating absence of movement throughout the ejection phase. (Fig. 6A.) Similarly, upward movement occurs only during the isometric relaxation phase and the filling phase is represented only by a horizontal segment. We are uncertain as to the cause of such a curve. It

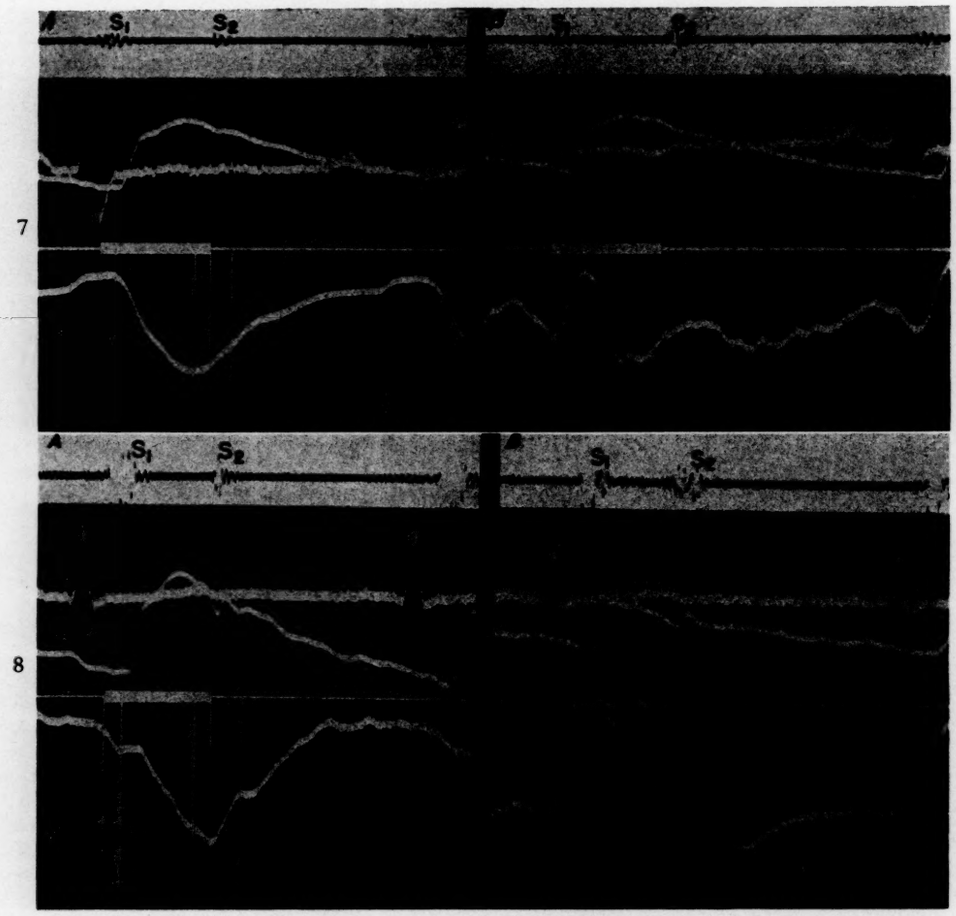

FIG. 7. Ventricular electrokymogram in myocardial infarction (partial reversal of pulsation). A, upper left ventricular curve is normal; B, lower left ventricular curve in left oblique view shows partial reversal of pulsation with paradoxic upward movement in early systole. This begins during isometric contraction (phase 1–2) and terminates early in the ejection phase. The abnormal movement was not observed in the postero-anterior view. Note diminished filling in diastole.

FIG. 8. Ventricular electrokymogram in myocardial infarction (partial reversal of pulsation). A, mid-left ventricular curve is fairly normal except for slight delay in the downward movement during ejection; B, lower left ventricular curve shows prominent upward movement during isometric contraction and early ejection with delayed onset of downward movement during ejection, indicating partial reversal of pulsation during systole. At the end of isometric relaxation (line 5) a paradoxic diastolic collapse occurs.

should be emphasized that when such ventricular border motion is viewed fluoroscopically the visual impression is gained of normal inward or mesial movement in systole although actually it occurs during the isometric phase instead of the ejection phase.

Partial Reversal of Pulsation in Systole. The majority of cases of myocardial infarction show this type of abnormal contraction. (Figs. 7 and 8.) Outward movement of the ventricular border, represented by upward movement of the kymographic curve, occurs during early, mid or late systole. The upward movement may begin in the isometric phase or at the onset of ejection and continue for a short interval into the ejection phase. It is then terminated abruptly by normal downward or mesial movement. The duration of the upward movement generally exceeds 0.08 second, differentiating it from a positional change which may produce upward movement in early systole lasting up to 0.06 second.[6] Less frequently, the paradoxic upward movement occurs in mid or late systole and is preceded by normal downward movement in the early ejection phase.

Another type of abnormal ventricular con-

traction is a delay in the onset of the downward movement in the ejection phase. The recorded curve shows neither upward nor downward movement during the early ejection phase but there is merely a horizontal segment lasting for 0.08 or 0.10 second. When ejection does begin, it produces normal rapid downward movement of the curve. Another variant of this type of delayed systole is recorded as a retardation in the speed of the downward movement. In this type of abnormality the downward movement during the early ejection phase is distinctly less steep and its descent is more gradual than that recorded over the adjacent normal segments, indicating retardation in the rapidity of inward movement of the ventricular wall. In the latter part of ejection the downward movement may become normal and proceed at a rapid rate. Both of these types of curves are indicative of delayed ventricular ejection and are often recorded in the transitional zone between normal and infarcted myocardium. They represent a degree of impaired ventricular contraction which lies between normal contraction and reversal of pulsation.

The differentiation of early transitory reversal of systolic pulsation from upward movement of the curve due to positional factors is of great practical clinical importance. Positional changes due to traction and twisting motion of the heart may produce lateral movement of the heart which displaces the ventricular border inward or outward, producing downward or upward movement of the electrokymographic tracing. This may occur either in the isometric contraction phase or beginning of the ejection phase. Another possible cause for the physiologic outward movement of the left ventricular wall at the beginning of systole is the fact that contraction of the interventricular septum precedes contraction of the free wall of the left ventricle. This unopposed initial contraction of the septum, which has been demonstrated by angiocardiographic methods,[27–29] may result in shortening of the heart in its longitudinal axis and temporary bulging of the walls in its transverse axis. This is recorded electrokymographically as a transitory upward movement of the curve.

In our experience[6,7] and in that of other observers[30] the duration of this upward movement of the curve in the ejection phase due to these physiologic factors rarely exceeds 0.06 second. In fact we have rarely seen upward movement beginning in the isometric phase and continuing into the ejection phase for a total duration of more than 0.06 second. We have come to regard any upward movement lasting for 0.08 second or more as pathologic and indicative of impaired ventricular contraction.

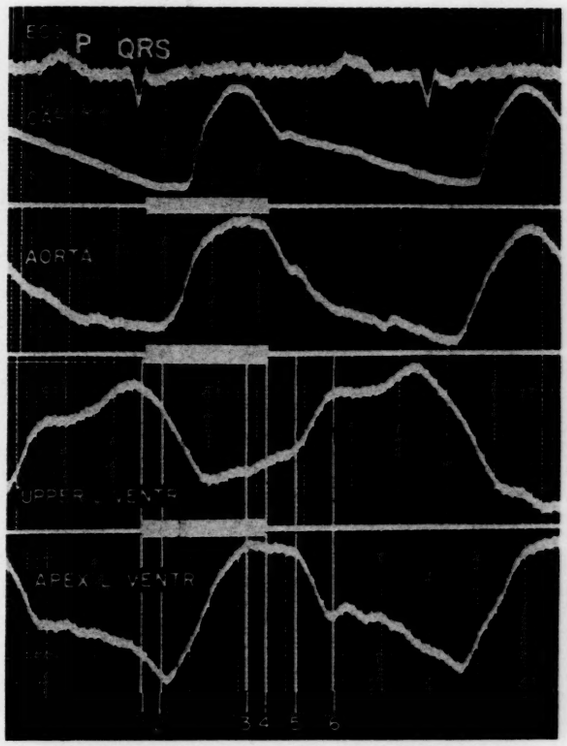

FIG. 9. Ventricular electrokymogram in ventricular aneurysm. (Complete reversal of pulsation.) The upper left ventricular curve is fairly normal except that the downward movement during systole terminates early in the ejection phase. The lower left ventricular curve taken at the site of the aneurysm shows complete reversal of pulsation with paradoxic upward movement beginning at the onset of ejection (line 2) and sustained until the end of isometric relaxation (line 5). Note that diastolic collapse occurs at time of rapid filling of upper left ventricle (lines 5–6). The paradoxic curve resembles the normal aortic kymogram. (With permission of the Editor of *Circulation*.)

Complete Reversal of Pulsation. In this abnormality there is reversal of normal direction of ventricular movement during systole and diastole. (Figs. 5B, 6B and 9.) At the onset of systole there is a sharp rise of the curve which generally begins during the isometric phase when the intraventricular pressure rises. The paradoxic upward movement is sustained during the entire duration of systole and is followed by paradoxic downward movement during diastole. Characteristically, this type of curve resembles an arterial pulse tracing. In some instances the

reversed pulsation does not begin until the onset of the ejection phase. In this type there is generally prominent upward movement in presystole during auricular contraction, followed by downward movement during the isometric phase of systole and upward paradoxic movement during the ejection phase. There is also abnormal downward movement during the filling phase of diastole.

In another variant of this group there is sharp upward movement in the isometric and early ejection phases. Then the upward portion of the curve is not maintained as a plateau but instead there is a slow gradual descent of the curve during late ejection and continuing into early diastole. At the end of the isometric relaxation phase, when the mitral valve opens and filling of the ventricle begins, a sharp collapse or paradoxic downward movement of the curve occurs. Several different types of abnormal curves may be recorded in the same patient from different segments of the left ventricle. Typical complete reversal during systole and diastole may be recorded at the apex and either partial reversal or absence of pulsation in the mid or upper left ventricular segments.

All the abnormalities described can be attributed to weakening of the left ventricular wall in the infarcted area, which shows outward bulging during systole and collapse of the wall during diastole. The outward bulge may appear during the isometric phase when intraventricular pressure rises suddenly or during the early ejection phase. It may be sustained for the entire duration of systole or occupy only part of systole. In the latter type the curve during diastole may be normal or show very little filling. In the former (complete reversal) there is inward movement during the filling phase due to collapse of the infarcted segment when intraventricular pressure falls. In partial reversal of pulsation there may be sharp upward movement of the curve confined solely to the isometric relaxation phase. (Fig. 6A.) An explanation of this phenomenon may be that when the aortic cusps close a sudden hydrostatic thrust or rebound is reflected against the residual blood in the ventricular cavity, causing outward movement of the diseased segment of the ventricle.

Although these recorded abnormalities in ventricular contraction indicate that the involved ventricular wall acts dynamically as an aneurysm, the size of the left ventricle may be normal and there may be no localized bulge or dilatation on ordinary x-ray examination. The outward bulge occurs only during systole and can be visualized fluoroscopically[31] as well as by the roentgenkymogram[26] and cinematography.[31]

Reversal of pulsation during the early ejection phase is often associated with exaggeration of the upward movement of the ventricular curve normally recorded in presystole during the phase of auricular contraction. (Fig. 10A.) This finding generally occurs in the presence of marked dilation of the ventricles and auricles and heart failure. Its presence therefore suggests increased contraction of the left auricle. The prominent filling movement of the left ventricle during auricular systole suggests an increased contraction of the dilated left auricle against an overdistended left ventricle due to an increased diastolic volume. The prominent upward movement in presystole may continue uninterruptedly into the paradoxic upward movement in the isometric phase.

Reversal of ventricular pulsation is generally best recorded in the posteroanterior view but may also be recorded in a slight left or right oblique position (10 to 15 degree rotation). Although it is more common in anterior than in posterior wall infarction, the presence and location of the abnormal contraction may not aid in localization of the myocardial infarct. This observation, although at variance with that of Luisada and Fleischner,[23] has been corroborated recently by Schwedel, Samet and Mednick.[25] Our studies also have indicated that in posterior or basal as well as in anterior wall infarction the abnormal contraction of the left ventricle is recorded best in the posteroanterior position. This is difficult to explain when it is remembered that the abnormal contractions produced by a posterior basal infarct resting on the diaphragm are recorded from the anterolateral aspect of the left ventricle in the posteroanterior position. We made similar observations in previous studies[32] based on correlation of the roentgenkymogram and electrocardiogram. These combined electrokymographic and roentgenkymographic studies have led us to believe that the abnormal ventricular movements observed by these methods may not be recorded from the actual infarcted segments but at some distance from them. It was speculated that transmission of the abnormal contractile movements in the ventricular wall away from the infarcted segment was due to the spiral arrangement of the ventricular muscle

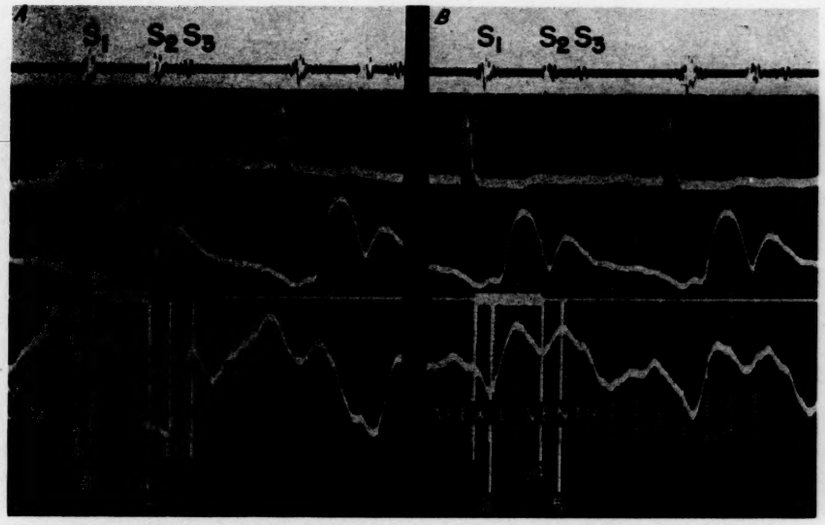

FIG. 10. Ventricular electrokymogram in hypertensive heart disease with marked dilatation of left ventricle and congestive failure. A, vertical time lines in this figure equal 0.10 second. The mid left ventricular curve is fairly normal. There is exaggerated upward movement in presystole due to increased auricular contraction associated with heart failure. The transient upward movement in early ejection beginning at line 2 lasts for about 0.06 second and is therefore within normal limits. Note diastolic rebound beginning with third heart sound (line 6). B, the lower left ventricular curve is very abnormal showing paradoxic movement with almost complete reversal of pulsation. The paradoxic upward movement begins at the onset of ejection (line 2) and reaches its peak at the height of ejection. A second smaller upward movement occurs during isometric relaxation (4–5) and is followed with early diastolic collapse. This curve indicates severe myocardial damage with impaired ventricular contraction and is suggestive of antecedent infarction despite the negative past history.

bundles which have attachments to both surfaces of the heart.

It would seem logical to compare the reversed or paradoxic ventricular pulsation following myocardial infarction in man with that which occurs following experimental coronary artery ligation. It has been demonstrated by Tenant and Wiggers[33] and by Prinzmetal and co-workers[34] that a myocardial segment rendered ischemic by coronary artery ligation ceases to contract within a few seconds. This leads to ballooning of the ventricular wall which may be sustained throughout systole or for only a short period in early or late systole. The similarity to the events in clinical myocardial infarction is evident.

The factors which determine the magnitude of the reversal of pulsation, that is, whether it is incomplete or complete, are not well understood. Experimentally it was noted by Corday and co-workers[34] that following coronary artery ligation ballooning of the ischemic ventricular wall may disappear shortly if the ligated vessel was small or it may come and go for unknown reasons. Following ligation of a large coronary vessel ballooning was more constant. This suggests that complete reversal of pulsation in clinical coronary occlusion occurs in the presence of extensive infarction. Furthermore, the investigators were able to alter the degree and extent of ballooning of the ischemic area by reducing the blood pressure to shock levels and increasing the coronary insufficiency. By this procedure it was possible to convert late systolic ballooning into complete systolic ballooning. Restoration of normal blood pressure resulted in complete or partial disappearance of the ballooning. These experiments indicate that even after a major coronary artery ligation normal ventricular contractility can be maintained or restored by maintaining an adequate collateral circulation.

In clinical coronary occlusion reversal of pulsation may appear soon after the clinical attack of myocardial infarction. In our past experience with the roentgenkymogram[26,32] reversal was observed as early as the first week. It was often preceded by localized diminution or

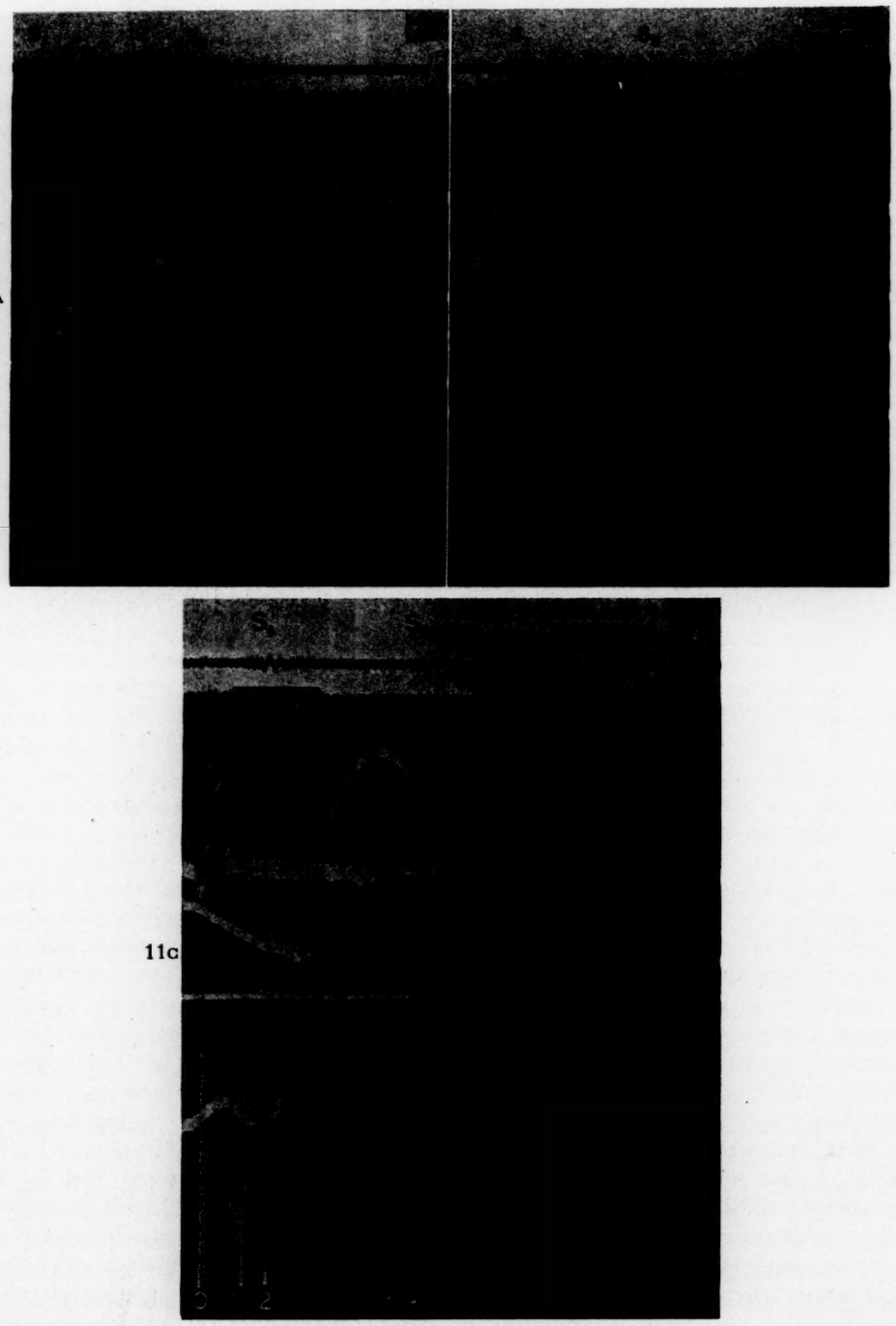

FIG. 11. Abnormal ventricular movement in congenital pulmonic stenosis exhibiting paradoxic pulsation fluoroscopically. A, upper left cardiac border shows normal left ventricular curve; B, apex of heart—note that during period of systole there are two downward-directed and two upward-directed serrations suggesting abnormal left ventricular pulsation. However, comparison with electrokymogram of right cardiac border (C) shows the curves to be identical. This indicates clearly that the apex of the heart is formed by the right ventricle and its overlying right auricle. Thus in B and C the first upward segment (0–1) represents right auricular contraction, the first downward serration (1–2) represents the isometric contraction phase of the right ventricle, the second upward wave (line 2) is the onset of right ventricular ejection and the third upward wave (4–5) is either right auricular filling or the isometric relaxation period of the right ventricle. Visually, these movements are easily mistaken for paradoxic pulsation. Note, also, that the major component of the second heart sound is caused by the closure of the pulmonic valves, since the carotid incisura follows the major deflections of the second sound.

absence of pulsation and partial or complete reversal appeared several days later. Regression of the abnormalities also occurred in the same manner; reversal was often replaced first by diminished pulsation and then by normal pulsation following healing of the infarct. In a majority of the cases, however, reversal was permanent and persisted even when the electrocardiographic pattern of infarction disappeared. For this reason the presence of these abnormalities in the electrokymogram may be diagnostic of antecedent myocardial infarction even when the electrocardiogram is atypical (Fig. 7) or in the absence of a typical clinical history.[6]

It has been reported[30,36] that reversed or paradoxic pulsations of the left ventricle may occur in normal individuals or in the presence of cardiac lesions other than myocardial infarction such as aortic insufficiency and patent ductus arteriosus. Our experience has been that, with rare exceptions, when significant abnormalities in the left ventricular contraction curve were recorded there was always a diseased ventricular myocardium. (Fig. 10.) This does not necessarily imply myocardial infarction specifically but may be the result of localized myocardial disease or ventricular dilation due to other causes, notably ischemic,[25] infectious and metabolic disturbances.[37] Nevertheless, in the great majority of instances when paradoxic pulsations are recorded, it can be inferred that myocardial infarction has occurred in the past. In fact it seems to us that the greatest clinical application of electrokymography thus far has been in the detection of localized abnormalities of ventricular contraction due to antecedent myocardial infarction. The sensitivity of the instrument is such that the recorded abnormalities frequently antedate or outlast the confirmatory findings in the electrocardiogram or roentgenkymogram.

We have never observed paradoxic or reversed pulsations in a normal individual. We have observed it in one case of luetic aortic insufficiency, one case of hypertensive heart disease with marked left ventricular dilation (Fig. 10) and one case of rheumatic aortic insufficiency. In the first case, however, the possibility existed of myocardial infarction due to coronary ostial stenosis. In the second case there was marked enlargement of the left ventricle probably associated with a diseased myocardium.

The presence of paradoxic pulsation may be suspected fluoroscopically but may not be confirmed by the electrokymogram. For example, delayed systolic ejection in a patient with aortic insufficiency and a damaged ventricular muscle was visualized erroneously as reversed pulsation. Visual examination of the ventricular movements has become a routine procedure and a well trained fluoroscopist can usually detect most abnormalities of ventricular contraction. However, the procedure is not infallible; and when an apparent reversed or paradoxic movement is visualized, it should be confirmed by a graphic recording.

Another source of erroneous diagnosis of paradoxic pulsation is found in certain cases of congenital heart disease. In right ventricular hypertrophy the right ventricle may enlarge to the left and displace the left ventricle upward. The apex of the heart may thus be formed by the hypertrophied right ventricle rather than the left ventricle. In one such case of pulmonic stenosis the pulsations of the left border appeared paradoxic. On the electrokymogram, however, it was noted that the movements of the lower left cardiac border were identical in appearance and timing with those of the right border. (Fig. 11.) Since the movements of the enlarged right auricle were superimposed on those of the right ventricle, the inward movement of the lower left border preceded that of the upper left ventricular border and visually simulated reversal of ventricular pulsation. Such careful analysis of the movements of all segments of the heart borders is necessary for the proper diagnosis of reversal of ventricular pulsations due to myocardial infarction.

Recording of reversal of pulsation localized over the upper segment of the left ventricular border should be viewed with suspicion. In the ventricular segment adjacent to the left auricular appendage auricular movements may be superimposed on the ventricular curve and produce apparent reversal of pulsation. A false reversal of ventricular movement also may be produced in normal individuals by the Valsalva maneuver. If the patient strains against a closed glottis while holding his breath, the rise in intrapleural pressure associated with this maneuver may result not only in diminished amplitude of ventricular pulsation but also in reversal of direction of movement.

MYASTHENIA GRAVIS

Distinctive abnormalities of ventricular movement may be observed in conditions other than

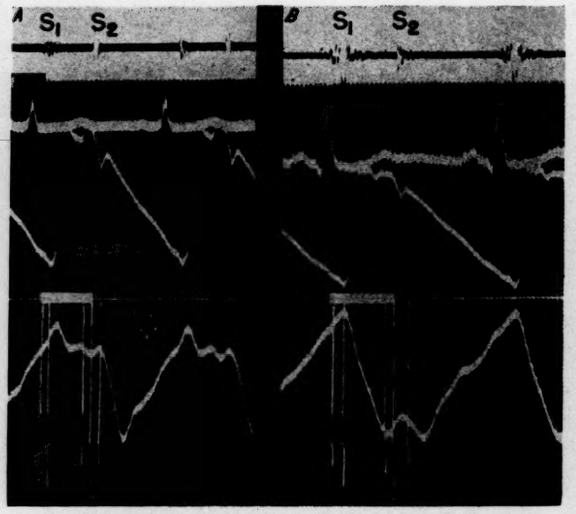

FIG. 12. Myasthenia gravis. A, before treatment, defective left ventricular contraction is demonstrated by the horizontal segment in the latter half of systole (phase 2–3). This is followed with a striking diastolic collapse in early diastole (line 5) and fairly normal filling in the latter part of diastole. B, after treatment with ACTH for one week the left ventricular curve is now normal in both the systolic and diastolic phases.

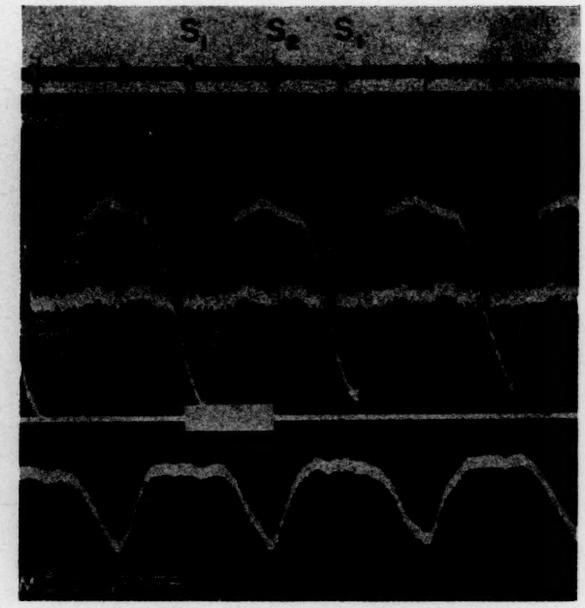

FIG. 13. Constrictive pericarditis. The left ventricular electrokymogram illustrates the typical V-shaped curves separated by flat plateaus described in this condition. The downward limb of the curve occurs during ejection and the upward limb during isometric relaxation and early diastole. No filling movement occurs in the latter part of diastole. The flat plateau between the two limbs is composed of a horizontal segment during impaired filling which is continuous with the flat segment representing isometric contraction. Note, also, that the carotid pulse curve is impure probably due to mixed arterial and venous pulsation.

myocardial infarction such as myasthenia gravis[38] and constrictive pericarditis.[39] In a small series of cases of myasthenia gravis we have noted marked disturbance in ventricular contraction in one case. In Figure 12 it will be noted that there is reversal of the normal sequence of contraction and relaxation of the left ventricle, which simulated myocardial infarction. It is of great interest that in this case all the abnormalities in left ventricular contraction disappeared almost completely after treatment with ACTH for one week which produced a temporary clinical remission.[40] This subject will be dealt with in greater detail in a forthcoming publication.[37]

CONSTRICTIVE PERICARDITIS

The recording of ventricular pulsation is often of diagnostic value in constrictive pericarditis since the electrokymogram may show a typical deformity of left ventricular border motion.[39,41] The restriction of ventricular movement in this condition may result in characteristic V-shaped ventricular curves separated by flat plateaus. (Fig. 13.) Both the downward (ejection) limb and upward (filling) limb of the curve are steep but the latter is steeper than the ejection limb. No secondary small serrations are seen in early systole and diastole as in the normal ventricular curve. This type of abnormal curve, indicative of impaired ventricular filling, has been noted to disappear following surgical cure of the constrictive pericarditis. It is of interest that the characteristic plateau curve has been reported[13] in some apparently normal individuals, particularly in the presence of bradycardia.

This characteristic abnormality of ventricular pulsation is not recorded in all cases of constrictive pericarditis. In several instances we have observed[42] practically absent contractile movements over the entire extent or over a considerable segment of the left ventricular border which returned to normal after surgery. (Fig. 14.) On the other hand, the pulsations of the right cardiac border, which were mainly auricular in origin, were not significantly diminished.

VENTRICULAR ASYNCHRONISM

The electrokymogram is a valuable tool for detecting asynchronism of ventricular contraction in bundle branch block and Wolff-Parkin-

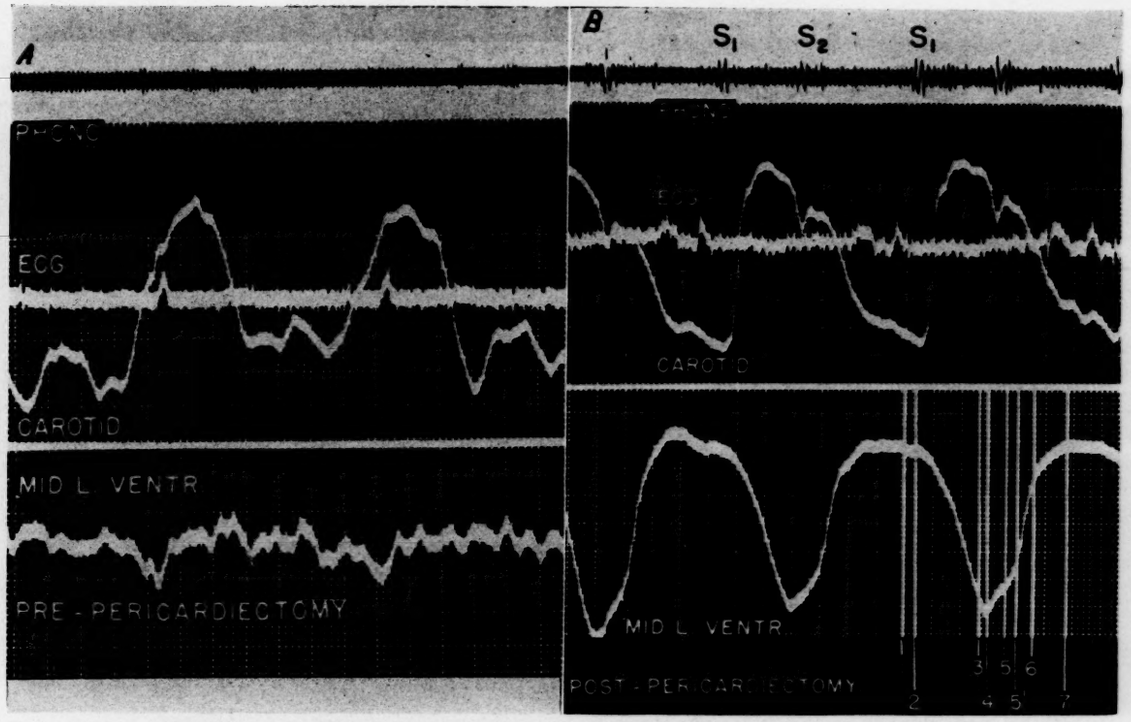

FIG. 14. Constrictive pericarditis. A, preoperative record. The left ventricular electrokymogram consists of numerous small fibrillatory movements despite maximal amplification. The encasement of the heart in this case resulted in almost complete obliteration of heart border movement. Note again the mixed type of curve obtained over the carotid artery and the almost invisible heart sound vibrations. B, three weeks after pericardiectomy which resulted in complete clinical cure. The left ventricular curve is now normal in form and amplitude. The heart sounds and carotid pulse curve are also normal.

son-White syndrome.[43] This may be determined by comparison of the onset of systole in the left and right ventricular curves but distortion of the onset of the curves by positional changes may make such analysis inaccurate. Therefore, use of the aortic and pulmonary artery curves is more satisfactory for determining the onset of the ejection phase in the left and right ventricle, respectively.[44] This subject therefore will be dealt with in a later review when great vessel motion will be discussed.

PULSUS ALTERNANS (MECHANICAL ALTERNANS)

The electrokymogram is ideally suited to depict the variations of filling and emptying of the heart chambers in mechanical alternans. Although the carotid pulse curve can be used as a graphic method for left ventricular alternans, it yields no information concerning the mechanical events in the right ventricle. Roentgenkymography has been employed in the past[45] but the curves obtained, particularly of the right cardiac border, are small, difficult to analyze, limited to one or two cycles and not integrated with other graphic events in the cardiac cycle.

Electrokymography lends itself to the study of the movements of all the heart chambers as well as the volumetric curves obtained from the aorta and pulmonary artery. Figure 15 is an excellent example of the alternating amplitudes of contraction which characterize mechanical alternans. Space does not permit of a detailed discussion of our cases but several interesting observations may be mentioned. It has been noted that the entire heart generally participates in the alternation. The right auricle and ventricle as well as the left show the characteristic changes, emphasizing the widespread disturbance in myocardial function. Moreover, all degrees of alternation may occur ranging from almost absent contraction to slight diminution in amplitude. The latter type may easily be undetected by other indirect methods of study. Our records also indicate that alternation in amplitude is accompanied with changes in form of the curve, which may be particularly pronounced in the isometric contraction and relaxation phases as well as during ejection and filling.

Although this phenomenon has been attributed to myocardial damage due to hyper-

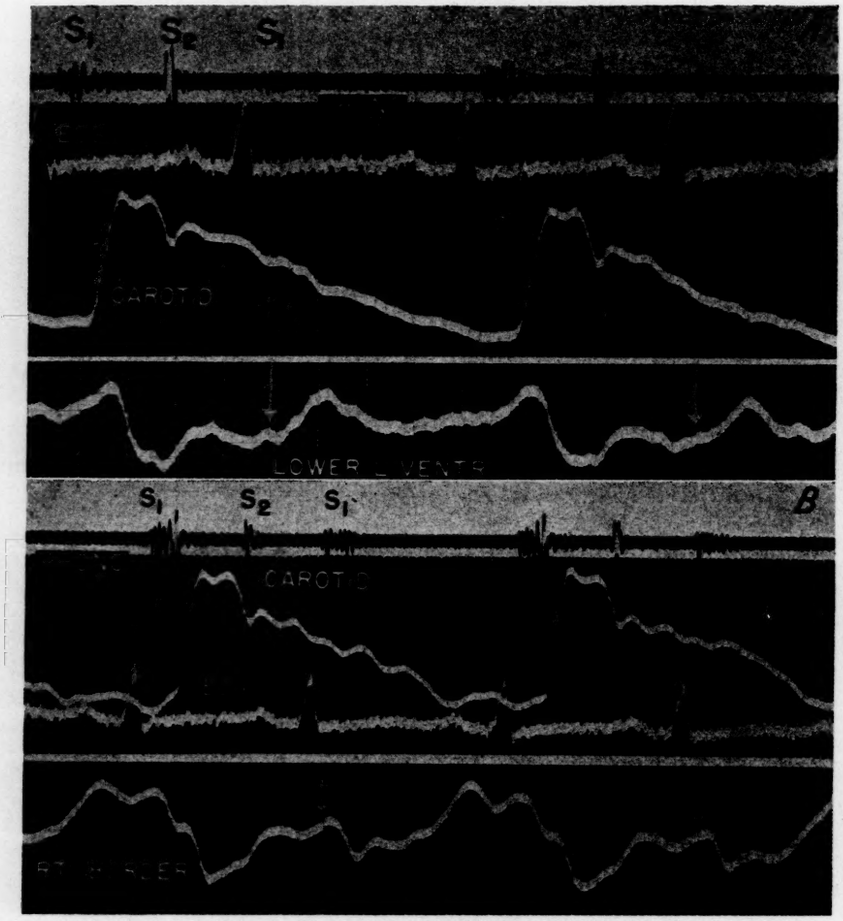

FIG. 15. Pulsus (mechanical) alternans. A, the left ventricular alternans is demonstrated by the alternation in amplitude and form of the curves. There is marked diminution in ejection during alternate cycles (arrow) resulting in a barely visible carotid pulse curve, diminished first sound and absent second sound. The filling phase is also markedly reduced. There is no concomitant electrical alternans. B, the electrokymogram of the right border demonstrates mechanical alternans of the right ventricle and probably also of the right auricle.

tension and coronary sclerosis, we have also seen it in advanced valvular heart disease. It has been reported[13] in electrokymograms of apparently normal individuals but we have observed it only in severe heart disease.

SUMMARY

In this review application of the electrokymographic method to the study of left ventricular border motion is discussed. The method has obvious limitations, principally because true volumetric curves are not obtained due to superimposed positional changes. It is necessary, therefore, to be cautious in interpreting the graphs and to become acquainted with the normal variations encountered. Nevertheless, continued experience with the method indicates that characteristic patterns may be evolved in normal and abnormal states.

From a physiologic standpoint the electrokymogram has been helpful in a better understanding of the events in the cardiac cycle. Demarcation of the various phases of mechanical systole and diastole has been aided immeasurably by simultaneous recordings with several graphic methods. It has thus been possible to study each phase of the cycle and integrate it with the serrations recorded in the electrokymogram. It is hoped that continued study along these lines will shed considerable light upon the less clearly understood phases, particularly isometric contraction and relaxation. Studies are already beginning to appear

on the effect of drugs such as digitalis on the mechanical behavior of the myocardium.

Clinically, the ventricular electrokymogram appears to be most useful in the detection of impaired myocardial action consequent to myocardial infarction and localized damage due to various pathologic states. Although the electrokymograph is by no means the simplest or most useful method for the determination of myocardial damage, we have encountered specific cases in which it has been most helpful. This applies particularly to cases of myocardial infarction associated with bundle branch block or doubtful electrocardiographic findings, or cases in which the electrocardiogram has returned to normal. In these instances unequivocal electrokymographic findings established the diagnosis.

Evidence is presented that the ventricular electrokymogram may yield valuable information concerning myocardial aberration in conditions such as hypertensive heart disease, coronary sclerosis, constrictive pericarditis, myasthenia gravis and congenital heart disease. Involvement of the entire heart in pulsus alternans is clearly demonstrated. In a subsequent review we shall discuss the findings in disturbances affecting the atria and great vessels, cardiac arrhythmias, ventricular asynchronism and valvular heart disease.

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Seminars on Congenital Heart Disease

Cardiac Catheterization in the Study of Congenital Cardiovascular Anomalies*

An Evaluation

AARON HIMMELSTEIN, M.D. *and* ANDRE COURNAND, M.D.
New York, New York

ADVANCES in our knowledge of congenital anomalies of the heart and large vessels have been the result largely of slow and patient collation of clinical and post-mortem findings, together with the broader application and improved interpretation of roentgenologic and electrocardiographic observations. As long as methods of treatment were wanting, this special branch of cardiology stimulated only academic interest. The surgical methods for the alleviation and cure of congenital heart disease which have been developed in the last twelve years have made accurate diagnosis and an understanding of the physiologic principles that govern the clinical manifestations and course of these malformations of prime practical importance.

During this period two new methods of exploration of the circulation have become available, i.e., cardiac catheterization and angiocardiography. Since these methods afford a means of identifying and delineating cardiac cavities and large vessels and also of studying cardiocirculatory dynamic processes in the living, their use became widespread.

It is our purpose in this article to make some pertinent inquiries concerning cardiac catheterization. We shall first discuss the fundamentals of this method as it applies to the problem of congenital heart disease. We shall then deal briefly with the specific information obtained in the most common cardiac malformations with regard to the diagnostic value of the findings and the physiopathologic insight provided. Finally, we shall discuss the risks entailed by the method. Such an inquiry should help decide whether the favor in which this method seems now to be generally held is justified, and also whether enthusiasm for its clinical application should not be somewhat tempered.

FUNDAMENTALS OF CARDIAC CATHETERIZATION

I. Basic Information on the Normal Circulation.

1. The post-natal closure of the foramen ovale and of the ductus arteriosus results in the anatomic and dynamic separation of the right auricle with its tributary venae cavae, the right ventricle and the pulmonary artery through which mixed venous blood with reduced oxygen content flows on the one side, from the left auricle and confluent pulmonary veins, the left ventricle and the aorta through which nearly completely oxygenated blood flows on the other.

2. If an individual's metabolic state remains unchanged, there will be little variation in the oxygen content of mixed venous samples taken from different parts of the right side of the heart and pulmonary artery; the composition of blood after its oxygenation in the lungs also is presumably constant as it goes through the left side of the heart and aorta.

3. Not only is the composition of the blood respiratory gases different in the right-sided structures as compared to their left-sided counterparts, but the range of blood pressures differs significantly. It is now well established that in normal man the blood pressure in the left auricle is higher by a few millimeters of mercury than in the right auricle; also that the systolic pressure in the left ventricle, and the systolic, diastolic and mean pressures in the aorta are several times higher than in the right

* From the Departments of Medicine and Surgery, Columbia University, College of Physicians and Surgeons, and the Cardio-Pulmonary Laboratory of the First Medical and Chest Services (Columbia University Division) Bellevue Hospital, New York, N. Y. The work discussed in this paper was supported by grants from the United States Public Health Service and the Life Insurance Medical Research Fund.

ventricle and the pulmonary artery, respectively. Hence, any abnormal communication between two adjacent cardiovascular structures should lead to a shunt of blood directed from left to right, unless abnormal dynamic conditions develop in the pulmonary circulation.

4. Since the amount of blood flowing through the aorta is equal to that flowing in the pulmonary artery, the large pressure differences are in great part related to a much smaller resistance in the pulmonary than in the systemic vascular bed. Furthermore the arteriolar and capillary bed of the pulmonary circulation is able to accommodate a fairly large increase in blood flow without significant increase of pressure in the main branches of the pulmonary artery.

5. The patterns of blood pressure curves in the auricles, ventricles and large vessels—aorta and pulmonary—are quite distinct.

These considerations are to be thoroughly understood in order to appreciate the nature of the data supplied by cardiac catheterization in congenital cardiovascular defects.

II. Nature of Data Obtained in Congenital Cardiovascular Anomalies. If one excepts rarely observed malformations, most congenital cardiac defects are characterized either by (1) an abnormal communication between two adjacent vascular structures (left and right auricle or ventricle, aorta and pulmonary artery); (2) a narrowing or atresia of the valve orifice leading from the auricle to the ventricle, or from the ventricle to the large vessel which originates from it; (3) an abnormal development, origin or drainage of large arterial and venous vessels; (4) an association of these anomalies in various combinations. Recognition of these different types of defects and study of their effects upon cardiocirculatory dynamics, is the domain of cardiac catheterization.

This method consists in the introduction of a radio-opaque flexible catheter of particular design into the venous system. Under fluoroscopic control the catheter is advanced into the heart and large vessels shadow. It is then possible (1) to follow the routes taken by the exploring tip, (2) to withdraw blood samples in the various locations it reaches for determination of oxygen content and saturation and (3) to record blood pressures in these various sites using appropriate manometric devices. This technic therefore yields: (1) X-ray visualization and identification by the position of the catheter of (*a*) cardiac and vascular structures, (*b*) of abnormal intracardiac and intervascular communications and (*c*) of abnormal venous drainage or arterial implantation; (2) approximate localization in the chambers of the right heart and in the pulmonary artery of the level at which the contamination of mixed venous blood by well oxygenated blood takes place; this contamination occurs only when the pressure conditions prevailing in the heart or in the large vessels favor the shunting of blood from left to right, and (3) measurement of blood pressures on both sides of an abnormal communication, across a stenotic area, as well as in all the other accessible cardiovascular structures.

Other data are essential to complete the exploration. Arterial blood samples are collected simultaneously through an indwelling needle placed in a peripheral artery; the determination of the O_2 content and saturation therein enables one to recognize the contamination of well oxygenated blood by some mixed venous blood shunting from the right to the left side of the heart. Furthermore, recording of arterial blood pressures through the same needle can be used for comparison with simultaneous recordings of intracardiac and large vessel blood pressures. Finally, determination of the oxygen uptake in the lungs obtained simultaneously with blood oxygen data in the heart and in a systemic artery permits one to calculate the approximate magnitude of blood flow in different parts of the circulation, and blood shunts through abnormal communications, by making use of appropriate formulas.

III. Validity of the Data. Several conditions must be met if the results of cardiac catheterization are to be considered valid and justifiable of interpretation. First, a steady state of the circulation and respiration must be attained. In young children a general anesthetic may be required in order to maintain this state during the entire procedure. Secondly, blood samplings in the same large vessels and cardiac cavities must be numerous and taken in rapid succession in the various locations; the data thus afforded are more easily interpreted whenever the persistence of stream line flow beyond an abnormal communication prevents thorough and homogeneous blood mixing. Thirdly, blood pressure tracings, readily visible on a cathode-ray oscilloscope or on a direct writing recorder or on any other appropriate device, should be recorded simultaneously from the heart or large vessels and from a peripheral artery. Finally, the gas

analyses in the blood samples withdrawn should be performed rapidly and the results made available to the investigating team; this will permit repeat blood sampling in crucial locations if indicated. The recent development of an oximeter with special cuvettes for direct and immediate determination of the oxygen saturation in blood withdrawn constitutes an important step in simplifying the method.

It is essential to insist that all these data be considered in relation to each other and integrated judiciously, and that incomplete or single observations are often worthless. Thus, (1) the form of pressure tracings helps confirm the exact location of the exploring tip of the catheter, since cyclic pressure variations in the auricles, ventricles and large vessels yield characteristic curves; (2) the results of blood respiratory gas determination may be meaningless if the exact source of the withdrawn samples cannot be ascertained by location of the catheter, and the pattern of pressure curves obtained simultaneously; (3) the direction of shunts and the respective magnitude of pulmonary and systemic flow, as derived from blood gas determinations, should be compatible with the gradients of pressure measured across adjacent abnormal communications or in contiguous cardiovascular structures.

IV. Limits of Interpretation. With data supplied by cardiac catheterization, technically satisfactory and correctly integrated and interpreted, it should be possible (1) to detect the presence of abnormal communications; (2) to estimate the magnitude and direction of blood shunts and also the approximate volume of blood flowing in the pulmonary and aortic systems, respectively; (3) to recognize the presence of stenotic areas and the degree of hypertension in the pulmonary vascular system; (4) to discover aberrant venous drainage and malpositions and abnormal course of the aorta. However, even though the technical facilities and skill are adequate, interpretation of the data is not always simple.

A few examples of the more frequent difficulties encountered follow: (1) A difference in the oxygen content of blood withdrawn from two separate cavities of the right heart may be due to different abnormalities; (2) the demonstration of a shunt in the same general location may be related to two entirely different anatomic defects; (3) calculations of systemic and pulmonic blood flow and of blood shunts are to be considered at best as approximations. It is impossible to ascertain sometimes, even with withdrawal of multiple blood samples from the same cardiovascular structure, whether the stream of a shunt is adequately mixed with the main stream of blood flowing through the cardiac chambers of the large vessels. Furthermore, in cases in which collateral circulation supplied by the aortic system, i.e., bronchial, intercostal arteries, contributes a large proportion of the pulmonary circulation, it is also impossible to calculate the respective volume of the column of blood flowing through the pulmonary artery and through the anastomatic system, since there is no way to estimate the amount of oxygen taken up respectively by each. (4) Unsuccessful attempts at directing the tip of the catheter into a large vessel or an abnormal communication cannot be considered as evidence for or against stenosis or malposition.

In order to solve such difficulties it is often essential that the results of cardiac catheterization be compared with and often interpreted in the light of observations obtained by careful physical, x-ray and electrocardiographic examinations. The importance of this cannot be overemphasized.

RESULTS

If one excludes a few rare forms of congenital heart defects, four relatively simple physiopathologic patterns emerge from the analysis of data: (1) Single abnormal communication between left- and right-sided cardiovascular structures; (2) pulmonic stenosis with normally located aortic root, the stenosis being isolated or associated with an abnormal communication; (3) pulmonic stenosis with dextroposition of the aorta and (4) dextroposition of the aorta without pulmonic stenosis. Coarctation of the aorta has not been included in this classification since cardiac catheterization has no place in its study.

The essential findings concerning the dynamics of the circulation in these four essential patterns and the diagnostic value of the method are now briefly discussed.

I. Single Abnormal Communication. Any abnormal communication between adjacent cardiac cavities or between the aorta and the pulmonary artery favors the development of a blood shunt, initially from left to right.

1. Interauricular septal defect: The persistence of an ostium primum or secundum allows blood to pass from the left to the right auricle as a

result of the normal pressure gradient existing between these two cavities. The abnormal communication may be demonstrated *directly* by introducing the tip of the catheter through the defect, or *indirectly* by demonstrating the contamination of mixed venous blood by oxygenated blood at the level of the right auricle. If the tip of the catheter has not been introduced into the left auricle or a pulmonary vein draining directly into the right auricle, the exact location of this contamination cannot be exactly determined. According to the magnitude of the blood shunt the pulmonary blood flow varies greatly; it may sometimes reach three times the systemic blood flow. The pulmonary arterial pressure as a rule remains normal or near normal but may increase significantly following the development of pulmonary vascular changes. It is rather exceptional, however, that right ventricular and right auricular dilatation lead up to reversal of blood flow through the interauricular septal defect, with significant reduction of the systemic arterial blood oxygen saturation.

As a rule the diagnosis of interauricular septal defect can be established on the basis of clinical findings. However, if in doubt, cardiac catheterization helps conclusively to eliminate other defects causing dilatation of the pulmonary artery associated with x-ray evidence of a normal or increased pulmonary blood flow, i.e., high interventricular septal defect, mild pulmonic stenosis, idiopathic dilatation of the pulmonary artery and primary pulmonary hypertension.

2. Interventricular septal defects: In the presence of the classical signs of Maladie de Roger cardiac catheterization is superfluous for the diagnosis. If resorted to, it would establish the presence of a left to right blood shunt at the level of the right ventricle, usually of small magnitude and without effect upon the right ventricular pressures.

In the type of interventricular septal defect located immediately below the semi-lunar valves, cardiac catheterization is of great diagnostic value. It permits (1) recognition of the blood shunt from left to right by demonstrating an increase in oxygen content in the right ventricle as compared to the right auricle, particularly in the samples of blood obtained in the infundibular area, and (2) documentation of the marked pulmonary arterial hypertension which always accompanies this malformation for reasons which are still not clear, since the increase in pulmonary blood flow, although significant, is usually not large enough to explain it.

The diagnoses to be discarded are those of malformations leading to dilatation of the pulmonary artery with evidence of large blood flow. They belong to the group just discussed and to be discussed immediately following.

3. Communication between the aorta and the pulmonary artery: Two defects lead to blood shunting from the aorta into the pulmonary artery; one which is frequent—the patent ductus arteriosus—is amenable to cure by ligation or division; the other very rare—aortic septal defect—appears still to be beyond the resources of surgery. As a rule the clinical diagnosis of patent ductus arteriosus is obvious; in some cases, however, it may remain in doubt.

Among the most helpful information supplied by cardiac catheterization one must list the direct demonstration of a patent ductus arteriosus by insertion of the tip of the catheter into this channel by way of the left pulmonary artery near its origin and the emergence of the tip in the descending thoracic aorta. Thus in the left anterior oblique position the opaque catheter appears as a cord subtending the arch of the aorta. If the catheter goes through an aortic septal defect, it would lie in the arch of the aorta. Indirect demonstration of the shunt of well oxygenated blood from the aorta to the pulmonary artery is provided by the finding of a considerable increase in the oxygen content in the latter vessel as compared to the oxygen content of the right ventricle and auricle. But analysis of the oxygen content in successive blood samples obtained from the two right chambers and from the pulmonary artery cannot differentiate an aortic septal defect from a patent ductus arteriosus. The direct demonstration of the course followed by the catheter therefore is the only pathognomonic finding. The blood pressures in the pulmonary artery may be normal or sometimes considerably elevated, but there appears to be no absolute relationship between the height of pressure, the size of the shunt which may be several times the systemic flow or the age of the subject. However, in adult patients atheromatous changes often occur in pulmonary vessels, causing an increase in pulmonary vascular resistance which is reflected in a rise of pulmonary artery pressure. As a result of this increased resistance the mag-

nitude of the aortopulmonary shunt diminishes, and in some instances this process may lead to a cyclic or continuous reversal of the direction of the blood shunt and to late cyanosis. In such cases the demonstration of a reduction of the blood oxygen saturation in the femoral arteries with maintenance of a normal oxygen saturation in the right brachial artery is pathognomonic.

If a patent ductus arteriosus is complicated by functional pulmonary valve incompetence during diastole, blood with a high oxygen content regurgitates into the right ventricle, and the average oxygen content in this cavity increases significantly above that of the right auricle. Under such circumstances, on the basis of blood gas determinations, it may be difficult to separate this condition from (1) a high interventricular septal defect with persistence of laminar flow in the pulmonary artery, and (2) a combination of patent ductus arteriosus with an interventricular septal defect. Confusion then may result from the analysis of data obtained by cardiac catheterization unless a very keen analysis is made of the character, location and propagation of murmurs present.

II. Pulmonic Stenosis with Normally Located Aortic Root. The problem of pulmonic stenosis not associated with dextroposition of the aorta has been completely reopened by the systematic investigation of congenital cardiac anomalies by cardiac catheterization. Recognition of the relative frequency of this lesion, until then little suspected, is one of the most important items to the credit of this method, particularly since these lesions are amenable to a special type of surgical intervention, i.e., pulmonic valvulotomy.

Whether the stenosis is simple or associated with septal defects, cardiac catheterization provides the characteristic findings in the form of a low or normal pulmonary arterial pressure with a moderate or considerable systolic hypertension in the right ventricle. The exact location at which the systolic pressure suddenly rises when the tip of the catheter is withdrawn from the pulmonary artery into the right ventricle, under fluoroscopic control, helps distinguish valvular from infundibular stenosis. In the former, the change is abrupt; in the latter the pressure tracings reveal an intermediate type in which the diastolic pressure is lower than in the pulmonary artery, and the systolic pressure lower than in the right ventricle; the sudden change to a high systolic pressure occurs near the tricuspid valve. Distinction between valvular and infundibular stenosis is important since different types of surgery may be selected for their relief.

1. Simple pulmonic stenosis: According to the degree of right ventricular systolic hypertension two essential forms may be isolated: (1) In the mild form, a common error is to suspect an atrial septal defect with small shunt, or a Maladie de Roger. This error should be easily dispelled on a clinical basis. In the presence of an aneurysmic dilatation of the pulmonary artery it can also be confused with idiopathic dilatation of the pulmonary artery, in which instance the systolic pressure in the right ventricle remains normal and is but somewhat reduced in the pulmonary artery. (2) In the severe forms of stenosis with reduced cardiac output and slow peripheral circulation, confusion with any other condition is unlikely as soon as it is demonstrated that the cyanosis is peripheral and therefore not associated with any reduction in the arterial blood oxygen saturation.

2. Pulmonic stenosis associated with septal defects: Two types have been isolated depending on whether the shunt is from left to right or in the reverse direction. The clinical signs of either the stenosis or the septal defect, more frequently interauricular than interventricular, may dominate the picture. Cardiac catheterization constitutes the keystone of the diagnosis in revealing the defect *directly*, the blood shunt *indirectly* and its normal direction from left to right. Pulmonic stenosis associated with an interauricular septal defect and reversal of shunt is one fairly common cause of the so-called "cyanotic forms of congenital heart disease." It should be distinguished from the Tetralogy of Fallot since pulmonary valvulotomy rather than a Blalock anastomosis is the rational surgical procedure. Cardiac catheterization in these cases provides direct evidence of pulmonary stenosis and of interauricular communication. However, contamination of mixed venous blood by oxygenated blood cannot be detected at any level in the right heart, but the systemic arterial blood oxygen saturation is markedly reduced. An important additional finding resides in the demonstration on the auricular pressure tracings of very high auricular systolic waves, the like of which, in congenital defects, is seen only in tricuspid stenosis. With the experience gained by comparing the findings of cardiac catheterization with the clinical history, the physical signs and electrocardiographic and roentgen-

ologic observations, this syndrome can now be established clinically without recourse to cardiac catheterization. The use of the method before deciding upon surgical intervention is, nontheless, greatly desirable as a confirmatory procedure.

3. Pulmonic stenosis with dextroposition of the aorta: The association of these two defects underlies the majority of congenital cardiac defects associated with cyanosis since birth. A high interventricular septal defect and a variable degree of ventricular hypertrophy constitute the two other terms of the most common form observed, i.e., Tetralogy of Fallot. The distinction between Tetralogy of Fallot, pulmonic atresia and pseudo truncus arteriosus, which is dependent upon the respective degrees of pulmonic stenosis and overriding of the aorta, may benefit from the use of cardiac catheterization.

With this method the probing tip of the catheter may directly demonstrate the overriding of the aorta, and may be advanced into a right or left aortic arch; however, failure to do so cannot be interpreted as evidence for exclusion of aortic dextroposition. Pulmonic stenosis is recognized by recordings of pressure tracings which often display the type characteristic of infundibular stenosis; however, failure to catheterize the pulmonary artery cannot be given as evidence in favor of a pulmonic atresia. The peak of systolic pressure in the right ventricle always reaches the level of pressure simultaneously recorded in the aorta or in a peripheral artery. This is true of all cases of dextroposition of the aorta. In exceptional cases differences in both directions have been reported although angiocardiography led one to suspect some degree of dextroposition of the aorta. It is not a mere question of nosologic classification to decide whether these are authentic cases with minimal dextroposition of no dynamic significance, or high ventricular septal defects with pulmonic stenosis, since in the latter instance valvulotomy rather than a Blalock anastomosis may be indicated. Determinations of the blood oxygen content in the right-sided cardiac cavities, in the pulmonary artery and in the aorta or a systemic artery are of great diagnostic value in demonstrating cross shunts of varying magnitude from the right ventricle to the aorta and from the left ventricle to the pulmonary artery. In cases of pulmonic atresia the contamination of arterial blood with mixed venous blood as a rule is extremely marked; and in rare cases of total transposition and of single ventricle with a rudimentary outlet chamber, the composition of blood in the catheterized ventricle is the same as in the aorta or a systemic artery.

In general, cardiac catheterization is not required to establish the diagnosis of Tetralogy of Fallot. However, in cases of cyanosis from birth in which the clinical findings differ from the classical description, special investigation is required before surgery is undertaken. This is generally true in cases in which (1) the cyanosis is mild, (2) the shape of the heart on x-ray films is unusual, or a post-stenotic dilatation of the pulmonary artery is present; (3) the reduction of pulmonary artery flow as identified by fluoroscopy is not striking and (4) evidence of considerable collateral circulation is derived from physical and roentgenologic findings.

4. Dextroposition of the aorta without pulmonic stenosis: Dextroposition of the aorta may sometimes develop without concomitant pulmonic stenosis. In its typical form known as Eisenmenger's syndrome, it is characterized by the shunting of large amounts of well oxygenated blood from the left ventricle into the pulmonary vascular system through the interventricular septal defect since the pulmonary vascular resistance is less than the systemic. Conversely, the amount of mixed venous blood flowing directly in the overriding aorta is usually very small and therefore cyanosis is absent. Cardiac catheterization is of considerable diagnostic value because one may directly demonstrate (1) dextroposition of the aorta, (2) an identical elevation of systolic pressure in the right ventricle, the pulmonary artery and the aorta and (3) a higher oxygen content in the pulmonary artery than in the right ventricle. Thus the diagnosis of a high interventricular septal defect with pulmonary hypertension, or of primary pulmonary hypertension may be eliminated. However, catheterization of both large vessels is not always accomplished.

In this type of malformation, and under hemodynamic conditions not always well defined, the resistance in the pulmonary vascular bed may increase to such an extent that the left to right shunt is progressively reduced and mixed venous blood flows in increasing amounts from the right ventricle to the dextroposed aorta. It is in such instances that clinical evidence of dilatation of the pulmonary artery associated with a re-

duction in the pulmonary blood flow and physiologic evidence of contamination of the arterial blood by mixed venous blood creates a picture which may simulate (1) a Tetralogy of Fallot with post-stenotic dilatation of the pulmonary artery; (2) a high interventricular septal defect with considerable pulmonary hypertension and reversal of shunt; (3) an idiopathic pulmonary hypertension with right to left blood flow through a patent foramen ovale. Cardiac catheterization is of considerable help in eliminating the first and the last of these diagnoses; but if the catheter tip cannot be introduced in the aorta, the second diagnosis cannot be entirely disposed of.

RISKS

Although most complications observed during and after cardiac catheterization in the course of study of congenital cardiac anomalies are of a minor character, an appreciation of its potential hazards is highly desirable.

1. Air emboli introduced into the catheter may be dangerous in cases in which hemodynamic conditions favor right to left shunts, since small air bubbles can be thrown into the systemic circulation.

2. Traumatic lesions of the endocardium with secondary thrombosis are another potential danger to be reckoned with. Although their frequent occurrence in the dog has been well documented, their demonstration in man has been very rare although they have been looked for by many investigators when the occasion for doing so presented itself.

3. Acute bouts of anoxia have been observed to follow catheterization of a markedly stenotic pulmonary valve in association with an interauricular or interventricular communication. Proper care should therefore be exercised in avoiding prolonged obstruction of such a stenotic area especially when cyanosis develops or its degree increases during manipulation of the catheter.

4. Pyrogenic reactions secondary to the introduction of foreign material can be avoided by proper cleaning and boiling of the catheter and the use of disposable plastic tubing.

5. Development of rhythm disturbances is by far the most important complication to consider. Since continuous electrocardiographic control has become a routine part of exploration with a catheter, it has been found that ectopic beats, ectopic rhythms, and tachycardias are not exceptional, and that conduction disturbances may develop although much less frequently. The arrhythmias are more apt to occur when the tip of the catheter is in the infundibular area of the right ventricle or is introduced into the left ventricle through a septal defect. Save in exceptional instances they cease immediately upon displacement of the catheter and have no clinical repercussions. In the presence of bursts of ventricular tachycardia, one should fear a marked drop in systemic pressure which can, in cases with cyanosis, bring about a considerable increase in arterial anoxia or the development of ventricular fibrillation. The mortality rate attributable to this technic can be estimated at about $\frac{1}{10}$ of 1 per cent, from figures collected in three laboratories where catheterizations have been performed nearly three thousand times. It would appear, therefore, that the risk is small indeed. It is, nonetheless, one that has to be taken into account before deciding to proceed with the technic.

CONCLUSION

Cardiac catheterization has a useful place in the study of congenital defects of the heart and large vessels provided certain criteria are met.

1. The physician in charge of the investigation should have skill in handling the catheter and should, of course, possess excellent clinical judgment. He should lead an alert and well integrated team efficiently trained in collecting gas and blood samples, recording blood pressures and detecting pulse rate and electrocardiographic changes. Finally, he should be served by a well organized laboratory.

2. Correct interpretation of data requires that they should always be compared with and often interpreted in the light of observations obtained after careful clinical and roentgenologic examinations. Cardiac catheterization is not a substitute for tried and sound clinical studies. Furthermore, an inadequate knowledge of the clinical manifestations often leads to overinterpretation of the data.

3. Since a potential risk is entailed in the use of the method, it is essential (*a*) to stress the importance of constant and instantaneous electrocardiographic control, (*b*) to exercise at all times caution and judgment, (*c*) to be able to check immediately potentially lethal manifestations by appropriate therapy.

4. Only those cases should be studied in which the diagnosis after careful and expert clinical

examination is still in doubt or in which a better documented diagnosis may be of aid in reaching a decision as to treatment.

5. To the credit of the method stand foremost: (*a*) The new meaning and significance that physiologic studies have given to physical and roentgenologic signs, so much so that clinicians familiar with it believe that cardiac catheterization is often unnecessary in order to arrive at a correct diagnosis; (*b*) the better appreciation it has provided of the clinical incidence of some defects in which surgical treatment may be indicated; (*c*) the tangible documentation it affords for judging the effect of new surgical procedures and (*d*) the great advance made in the understanding of the physiopathology of congenital cardiovascular defects.

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* The list of references is limited to a small number of original publications on subjects discussed in the paper and of review articles written by investigators with long experience with the cardiac catheterization technic.

Conference on Therapy

Low Cholesterol Diet in the Treatment of Atherosclerosis

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. GEORGE READER: Today we enjoy the privilege of having with us one of our old friends and colleagues, Dr. William Dock. Dr. Dock has long held the view that a relationship exists between dietary cholesterol and atherosclerosis. He is going to make the opening remarks in this conference on the role of diet in the treatment of atherosclerosis.

DR. WILLIAM DOCK: It is always a great pleasure to be invited back here, and especially to speak on a subject on which I have done no work at all. If one is asked to speak about his own work, it is pleasant to be sure, but not necessarily flattering, for there may be no one else interested in that field. Since some of the best work on this subject has been done right here, I regard it extremely complimentary to be asked to express my views.

I am taking for my text two lines from the fifth book of Lucretius "De rerum natura," which was written 2,000 years ago in the metropolis of the Roman republic, and I will read it in Latin, "tum penuria deinde cibi languentia Leto membra dabat, contra nunc rerum copia mersat." In free translation it reads as follows: "In the old days lack of food gave languishing limbs to Lethe, contrariwise today surfeit of things stifles us." Two thousand years ago the Romans knew they were eating themselves into their graves. This is apparently the normal fate of conquering countries. They take so much food away from their satellites that eventually they develop vascular disease and otherwise fall apart.

Studies on men, rabbits, dogs and chickens show clearly that overfeeding with animal products, and particularly with foods rich in fat and cholesterol, can cause atherosclerosis. Even overfeeding with vegetable fat, which is free of cholesterol, results in atherosclerosis in chickens, possibly in very old dogs, and in peculiarly susceptible people, but no one has produced atherosclerosis in rabbits or young dogs without cholesterol in the diet. In dogs it is necessary to reduce the protein intake and to provide a high fat intake in order to produce atherosclerosis without severe hypothyroidism. The latter, plus cholesterol feeding, rapidly induces arterial lesions.

At the present time, as you know, emphasis is placed on low fat content of diets rather than on low cholesterol content as a preventive measure. I think that the importance of cholesterol should not be minimized. Dr. Keys and his group in Minnesota have made the point that, in their region, the serum cholesterol level and the amount of cholesterol in the diet are unrelated. All the patients in the group they studied received cholesterol, although the amount they consumed differed. Dr. Keys takes the position that there is a relation between the amount of fat intake and atherosclerosis. In Minnesota, where a good part of the fat is supplied by eggs and dairy products, how he manages to distinguish low cholesterol from low fat diet is a mystery to me.

In those with high blood cholesterol levels and myocardial infarcts, diets low in fat and cholesterol reduce the blood levels of total cholesterol, and also the special fraction described by Gofman, which correlates with the tendency to atherosclerosis more closely than the total cholesterol. Here at Cornell you can determine whether diet influences cholesterol-phospholipid ratios in the blood or the ratio of cholesterol carried with beta-globulin to that carried with alpha-globulin. In those with atherosclerosis these ratios are high. Which of these values is the best guide to the tendency to develop atheromas, and hence the best guide

to the need for and results of diets, remains to be proved. As for therapy, there is no experimental evidence which shows that the additional intake of lipotropic substances, such as choline, inositol, methionine or lecithin alters the disease evoked by diet in dogs or rabbits. No supplements other than protein or thyroid material favorably modify the disease. If the patient and physician wish to employ a rational form of prophylaxis, capable in animals and man of slowing or even reversing deposition of cholesterol in the arterial intima, they will be limited to a diet low in cholesterol, fat and calories, adequate in protein, and in suitable cases supplemented with thyroid.

There is no close correlation between total blood cholesterol and the tendency to develop vascular disease. Certain fractions of cholesterol or certain relationships of the blood lipids have attracted attention. Dr. Forrest Kendall's group emphasizes the cholesterol-phospholipid ratio, which may be high when the blood cholesterol is high. Dr. Kellner's group have made the same observation. I believe that Dr. Barr has observed the rise of cholesterol in the beta-globulin fraction as compared with the cholesterol in the alpha-globulin fraction. These facts give ample proof that the total blood cholesterol is insufficient as a guide. One has to consider the distribution of the lipids and the ratios between different fractions. Dr. Gofman is quite sure that the fraction which floats in a certain method of ultracentrifugation, named Sf 12–20, is the fraction of cholesterol most directly related with the tendency toward vascular disease. It is noteworthy that Dr. Gofman's fraction falls off rapidly in the blood when the patient is placed on a diet low in fat and low in cholesterol. There is fairly good evidence that diet influences cholesterol-lipid relationships in the blood. The experience of Germany which went through a hunger period supplied information on this point. Recently Dr. Dedichen from Oslo was here in New York and presented an account which showed that in Oslo, when the Germans moved in and the calories moved out, the incidence of disease dropped off in a very striking fashion. In May, 1945, when re-alimentation began with the 3,600 calorie diet in place of an 1,800 calorie diet, it was only a few weeks before these diseases began to increase, and within a few months their incidence was back to the pre-war level. In Oslo the occurrence of coronary disease and thrombotic accidents following surgical intervention declined strikingly when the diet was poor in fat and calories. The role of diet in vascular diseases was well shown by data from the American Army in training in the United States and the British Army in training in Great Britain. We had a great deal of coronary disease in men under the age of thirty-five in our Army, while the British, consolidating their Army and Navy material, encountered much less coronary disease in young men, that is, men under thirty-five. Here are populations that are genetically much alike; both armies smoked their heads off; both were many months in training; but the types of alimentation in the two armies were substantially different. The incidence of coronary disease showed a marked difference.

The material I have cited supplies a reasonable basis for the view that a low fat and low cholesterol diet, with sufficient calories to maintain a person in a good state of nutrition, without obesity, will reduce the rate at which atherosclerosis develops. I believe it is also worth emphasizing that the diet should have a liberal protein content because, as shown in the dog experiments of Li and Freeman, deficiency in protein raised the blood cholesterol to high levels, whereas on liberal protein intake with the same amount of fat and cholesterol, the blood cholesterol levels scarcely rose at all.

It has been shown in rats that the cholesterol content of the skin will rise after increasing the fat content of the diet. It is well known that a great deal of cholesterol is made and broken down in the body daily, an amount beside which the dietary increment seems small, but it is possible that the dietary increment may have an effect on blood cholesterol and its partition fractions. Isotope studies with tagged cholesterol indicate that dietary cholesterol is the source of the atheroma in rabbits.

When it appears that our civilized diets cause disease, we always want to know if there is not some way to go on eating what we have always eaten and take something extra which will straighten everything out. In this case lipotropic factors have been suggested, something to add to the diet we are used to, which would make the cholesterol fractions fall into proper alignment as though we were on a low fat, low cholesterol intake. As I have already indicated, in dogs and rabbits the experimental disease cannot be modified by adding large quantities of such materials as choline, inositol and lecithin

to the diet. In chickens there is some evidence that these factors may exert a small influence. In the case of man there is one report to the effect that these factors added to the diet are very helpful, but the evidence is not impressive. I think that at the present time one can say that, while adding lipotropic agents to the diet is reasonable and is not likely to hurt the patient, the use of these factors as a substitute for a proper diet would be a mistake.

Incidentally, thyroid minimizes atherosclerosis in rabbits. In selected patients thyroid medication would seem to be worth trying if the cholesterol and phospholipids of the blood are being measured to test the value of therapy.

I would like to emphasize another aspect of diet, namely, the salt content. We have noted that in patients with coronary disease the initial symptoms may appear at a time when cardiac patients are prone to have attacks of pulmonary edema, that is, late at night. The patient goes to bed feeling fine; in one case he awakens with acute pulmonary edema; in the other case he awakens with the signs and symptoms of a myocardial infarction. We have also noted that in some of our patients such attacks have occurred after a day of high salt intake and a night's sleep, circumstances under which some of us note in ourselves a puffiness of the face and eyes. This is a fairly common experience in old men like myself, but it occurs in younger people, more often in women, I think, than in men. It indicates that while we are lying down, the salt and water we have accumulated shifts to the upper half of the body. The atheroma consists of the loose areolar tissue like that in the orbits, and we think the edema in such plaques can close down the coronary lumen. Symptoms appear which suggest coronary thrombosis. Repeated milder bouts of edema occurring this way every night may hasten the development of atherosclerosis, hemorrhage in the plaques or thrombosis in these areas. Low salt intake is, therefore, an appropriate dietary adjustment for a patient who has had a myocardial infarction. It also diminishes the chance of his developing myocardial failure.

To return to the problem of the low fat, low cholesterol intake, with adequate protein, how does one go about achieving this in practice? It is impossible to arrange a tasty low salt, low fat, low cholesterol diet, and it is hard to get the protein in. One may use beans and grains for vegetable protein. One may use meat that has been properly treated to take the sodium out, and with it the taste. Pot cheese can be desalted rather readily. This is made from skimmed milk, but again it is almost without flavor. The patient who accepts this form of management has to make the decision that he is going to eat to live rather than live to eat.

And this brings us to a fundamental question: At the ages at which myocardial infarction is likely to occur, is it worth while going on a diet just to postpone this sort of accident? Many people drive their cars dangerously, quite well aware of the risk. Dangerous occupations and dangerous sports are followed. Why not dangerous dining? I think it is unnecessary for everybody to go through life on a diet free of ice cream and omelet just to prolong his existence. There is a relevant statement in Guthrie's novel, "The Big Sky." One of the mountain men about to give up his beaver trapping concludes that when you are middle-aged, everything good that is going to happen to you, has already happened. I think it is a sobering and very sensible thought and makes one wonder whether it is worth while, at the time when your children are able to take care of themselves, for you to devote yourself to a way of living which you do not like, merely to try to prolong that tiresome existence for a greater span of years. Each person will have to make up his mind whether his obligations and inclinations make it worth while for him to follow such a regimen. Perhaps most people will make the same decision as some of my medical friends. They are convinced that the theory is correct, but they see no reason why they should adhere to the practice.

DR. READER: Dr. Wright, would you like to express your views on this matter?

DR. IRVING S. WRIGHT: I might make a few comments and ask a few questions at this point. If one were to be willing to live on one of these very disagreeable diets for the purpose of longevity, when should he begin that diet? Should he begin at the age of two, ten or twenty? Can he expect benefits from the diet if he begins when the process of atherosclerosis is already well developed? Is there any information on these questions? Of course, the level of the blood cholesterol can be affected by the diet, but that does not necessarily mean that the disease process or the longevity of the individual is being influenced.

Next I would like to present for discussion the fact that some individuals can live on a very

high fat and high cholesterol diet for many years without developing atherosclerosis. I know of a number of such individuals. I recall one in particular who was forced on such a diet by an ulcer, starting at the age of twenty-one. Now, at the age of eighty-three, he is doing very well and takes a three-mile walk every day. What differentiates those who are readily affected by high cholesterol from those who indulge in high cholesterol with impunity?

Atherosclerosis and sex are closely linked. Females develop atherosclerosis and the secondary damage from it later than males. This point is confirmed by practically every study dealing with it. Some years ago we studied a fairly large group at the Macy department store for evidence of atherosclerosis in the lower extremities. We found that in every age group there was a higher incidence of atherosclerosis in males than in females, the comparisons having been made in individuals of both sexes doing the same kind of work and having been engaged in the occupation more than ten years. The difference between the two sexes was also shown by the high incidence of the more severe grades of atherosclerosis, 3+ and 4+. As detected by x-rays, these were about ten times as frequent in the males as in the females. The same sex relationship is shown in the studies on coronary disease by the American Heart Association. The onset of the disease in the male is six to eight years earlier than in the female.

Lastly, I should like to refer to some work we carried out at the Welfare Hospital several years ago, which unfortunately was interrupted by the war. In a fairly large series of rabbits fed a standard cholesterol diet, the cholesterol accumulated in the aorta, but the female rabbits could be protected against this effect by estradiol or testosterone. The result was that the females developed only about one-fifth to one-sixth as much cholesterol in the aorta as the males. When the females were castrated, the hormones were no longer protective.

DR. READER: Dr. Dock, I believe you have an opinion on the sex difference in relation to atherosclerosis of the coronary arteries.

DR. DOCK: I did have an explanation for the sex difference in coronary disease but it may be wrong. Some years ago I studied the coronary vessels in male and female infants. The intima of the coronaries in males was much thicker. There seemed to be an actual anatomic difference between the sexes in these vessels. It did not hold true in all vessels. No difference was apparent in the aorta of the two sexes. Is that your impression, Dr. Kellner?

DR. AARON KELLNER: Yes. At autopsy the aorta of men and women shows little difference in the degree of atherosclerosis. However, the coronary vessels in women usually show less change than the vessels in men of the same age.

DR. DOCK: The explanation which I had offered on an anatomic basis does not appear to be the whole story. Others who have studied the coronaries anatomically have been less impressed with the difference in structure. Dr. Gofman believes that the difference between the sexes is biochemical; young men and middle-aged men have much more cholesterol of the Sf 12–20 fraction in the blood than women of the same age. Thus a biochemical difference in the lipids of the two sexes might explain differences in atherosclerosis in general but not the differences in the incidence of coronary sclerosis.

Whether smoking is or was responsible for the coronary differences in the two sexes, I do not know. There are those who think tobacco is important and place a great deal of emphasis on it.

The Health Department of the State of New York made a survey which revealed differences in the diet of men and women in industry, women showing a smaller intake of protein and fat than men; women eat far fewer eggs and less meat than do men in our population.

As Dr. Wright suggested, endocrine influences may play quite an important role.

Among the questions which Dr. Wright raised there was one which I believe is never relevant to any of our arguments. It has the same meaning as the account of the man who lives to the age of 103, who always drank a great deal or did not drink at all. What he has done is considered important because he lived 103 years. It is not a sound argument. The habits of persons who have eaten all the eggs and ice cream they could get their hands on, and are still quite chipper at the age of eighty or ninety, do not prove that what they have been doing is good for all of us. The fact that Mrs. Robert Louis Stevenson lived with a tuberculous husband many years and failed to contract tuberculosis does not prove it is wise to live with a spouse who has open tuberculosis. The greater risk of the spouse developing tuberculosis is amply proved by statistical correlations. One cannot use individual cases as a basis for such generalizations.

DR. WRIGHT: I should like to ask just one more question. Does Dr. Dock have any evidence, or has there been any evidence accumulated from people on ulcer diets over long periods of time, which shows increased incidence of atherosclerosis?

DR. DOCK: There are some reports which show that the incidence of atherosclerosis in these cases is not higher.

DR. WRIGHT: That is what I thought. It is also why I asked the question.

DR. DOCK: Dr. Plotz put patients with angina and peptic ulcer on an ulcer diet, and he reported that after a very short time these patients had developed a great deal of coronary trouble. I wonder whether this result may not have been caused by a change in diet.

DR. WRIGHT: I take it, then, you would agree that the relation of cholesterol and atherosclerosis is not a matter of intake alone.

DR. DOCK: We would all agree that it is not just one factor that determines atherosclerosis. Neither hypertension, diet nor endocrine upset alone produces atherosclerosis. I should say a word about the problems in diagnosis. Most of the advanced atherosclerosis which we see in the abdominal aorta is not associated with coronary deaths and the patient may have died of carcinoma, not of the atherosclerosis. To be of clinical importance, atherosclerosis has to occur in a place where it makes itself felt, i.e., in the legs, the coronary arteries or the brain. If the site happens to be somewhere else, it can progress to a very severe grade without ever coming to the attention of the doctor until autopsy. We should bear in mind, therefore, that these patients who pay no particular attention to their diet and live long are not necessarily free of atherosclerosis but have good coronary arteries, good cerebral arteries and good arteries in the legs. Symptomatic vascular disease is one thing and anatomic vascular disease is something else. No matter how one approaches the problem, it is quite obvious that most of the people that live on our American high cholesterol diet do not die of arteriosclerosis. Only about 40 per cent succumb to this disease. In the days when tuberculosis and typhoid took a larger toll, the incidence of death from arteriosclerosis was much lower.

DR. READER: Dr. Barr, do you have comments at this point?

DR. DAVID BARR: Dr. Dock has taken as a text the thought that overeating is harmful. Many observers between the times of Lucretius and Dock have believed that surfeit of food leads not only to obesity and discomfort but also to a shortened life span. Clinicians of every era have held persistently to the idea that gluttons have a relatively high morbidity and mortality from vascular disease. Greater average longevity and relative freedom from vascular accidents have been repeatedly claimed for the spare and the frugal.

European statistics accumulated during the last war concerning the beneficial effect of short rations upon the occurrence of coronary accidents and thrombotic episodes following surgical operations have attracted widespread attention. Dedichen's impressive observations in Oslo were presented at a recent Macy conference and have been mentioned today by Drs. Dock and Wright. His statistics were carefully prepared. They are substantiated by somewhat less complete data from other countries and groups. They present a trend which would be anticipated from innumerable time-honored, clinical observations on the relationship of overeating to vascular disease. There appears no reason to doubt that in Oslo fewer vascular complications were encountered during the period of food restrictions.

Dedichen's figures have been cited as relevant to problems in the pathogenesis of atherosclerosis and today Dr. Dock has used them as evidence that diet influences cholesterol and lipid relationships in the blood. Without attempting to deny categorically the validity of this inference, I would submit that other conclusions might be drawn from the data. Two aspects of Dedichen's report have, I think, been too little emphasized.

The first is that deprivation diets affected the incidence both of coronary disease and of thromboembolic phenomena. Although coronary disease is predominantly dependent upon atherosclerosis and, as many of us suspect, closely related to defects in lipid metabolism, thromboses in the veins are not obviously dependent upon either factor. On the other hand, intraluminal clotting is almost as closely related to the overt accidents of coronary disease as it is to thromboembolic accidents. The most obvious inference to be drawn from Dedichen's discussions is that a low calorie, low fat diet diminishes the tendency to thrombosis and that surfeit increases it.

The second point concerns the time interval at which lessened incidence of vascular disease

was noted during deprivation and at which increase in vascular accidents developed following removal of dietary restrictions. In each instance the trend was apparent a few weeks following the change in diet. It would be remarkable indeed if a chronic process like atherosclerosis were to be modified so promptly. On the other hand, perceptible effects on intraluminal clotting might be expected at once.

The inferences to be drawn from Dedichen's work are relevant to the discussion of diet in atherosclerosis. Great stress has been placed in recent years upon low cholesterol content of corrective diets and for reasons which have been mentioned by Dr. Dock: cholesterol deposit is prominent in the lesions of atherosclerosis; patients suffering from conditions in which hypercholesterolemia is a factor may develop premature and excessive atheroma; animals not naturally subject to the disease may develop it during excessive ingestion of cholesterol. Logic would suggest a diminished intake of cholesterol as a corrective measure. Actually, as has been pointed out today, the demonstrable effects of decreasing or increasing cholesterol intake within the limits of human dietary habits are minimal. Diets almost free of cholesterol have little influence unless they have been accompanied with rigid restriction in the consumption of fat. As has been emphasized today, daily formation of cholesterol in the body of a normal individual grossly exceeds the amount consumed even in high cholesterol diets. Furthermore, a large part of the endogenous cholesterol arises in the liver, is excreted in the bile and is subject to the same metabolic processes as that contained in the food.

It may be fairly said that the beneficial effect of dietary restriction of cholesterol alone is not as yet established. The role of such restriction when the ingestion of both fat and cholesterol are greatly limited is undetermined. Under these circumstances one must ask whether there is justification for placing patients who are thought to have atherosclerosis on cholesterol-free diets which are extremely distasteful and entirely contrary to human habit and appetite.

Data from many current observations and from the clinical experience of more than 2,000 years indicate clearly that surfeit and gluttony are harmful. Statistical analyses indicate that the deprivation diets of wartime which like all low calorie diets must be low in fat tend to diminish the mortality from vascular disease. There is then at the present time ample reason for prescribing low calorie and thus low fat diets not only for the obese but also for those who are known to have or are suspected of having atherosclerosis. Since man is an atherosclerotic animal, and since the disease probably affects to some degree most men and women above the age of forty-five, the advice should not be limited to those who have suffered from the obvious complications of atheroma, but should be extended to a very large portion of the population. It may be stressed, however, that the present justification for such a regimen rests more firmly upon the clinically observed benefits deriving from frugality and the maintenance of normal weight, than upon demonstrated relationship to lipid metabolism or the pathogenesis of atherosclerosis.

DR. READER: I take it then that Dr. Barr recognizes a relationship between decreased intake of food over a long period of time and lowering of the incidence of atherosclerosis, without assigning the cause to any specific product of diet.

DR. DOCK: The emphasis is on fat now rather than on cholesterol, on obesity rather than on cholesterol alone. I called attention to two species, the young dog and young rabbit, to which cholesterol has to be fed to produce atherosclerosis. Man may behave differently, but in these two species the rate at which atherosclerosis develops, other things being equal, is related to the level of blood cholesterol.

DR. KELLNER: You included the rabbit in this but it is not true of the rabbit.

DR. DOCK: In rabbits, blood cholesterol elevations associated with atherosclerosis occur only if cholesterol is added to the diet. The figures of Wakelin and Taylor support such a relationship in the dog. What all the important features are in the human diet are not settled. I think it is fairly clear that dietary fat and cholesterol influence the levels of blood cholesterol in many people, in some species of animals, and the facts of geographical pathology strongly point to man being related to other mammals in this dietary relationship.

DR. READER: Dr. Tolstoi, do you have a comment?

DR. EDWARD TOLSTOI: The subject of the relation of diet to atherosclerosis, it seems to me, is in the fact-finding phase. It does not seem wise to expect fulfillment of promises.

About twenty-five years ago, under the

guidance of Dr. DuBois, we studied two healthy men whose diet consisted of nothing but protein and fat. Their eagerness for fat was very great. I recall they cut the fat off the meat. They had it melted and drank it with a soup spoon. I was fortunate to have the opportunity to study their chemical metabolism. The figures are probably lost, since the central interest was in the effect of meat, and I might add parenthetically that the meat caused no damage. There were a few chemical figures as by-products. Lipemia developed in these subjects. Blood, when drawn, looked like cream, and the cholesterol rose to 700 in one man, the Arctic explorer, Stefanson. The blood cholesterol was tested at monthly intervals. Probably one or two periods of ingestion of the fat in the diet might have no effect, but such feeding over a long period of time might result in elevated cholesterol levels. That is what happened in these subjects. When they resumed the so-called normal dietary, the blood content returned to normal levels. That did not puzzle me as much as the lipemia in the starvation era of the treatment of diabetes when patients on the Allen regimen were receiving a diet of 50 gm. of protein, about 30 gm. of carbohydrate and about 30 gm. of fat. Why they developed lipemia has continued to puzzle me to the present day. I understand lipemia develops in starvation.

DR. DOCK: Yes, and a high blood cholesterol.

DR. TOLSTOI: If there is also a high blood cholesterol, the whole problem seems to be in an almost hopeless state of confusion.

DR. KELLNER: In connection with your observation that starvation produces not only lipemia but also hypercholesterolemia, a comment of Dr. Kendall's may be of interest. In a recent conversation with him, he referred to a number of patients on a rice diet, a diet which is most extremely restricted. Some of these individuals developed a moderate decrease in cholesterol but the most interesting point is that in some instances their Sf 12–20 particles, the Gofman particles, which are the current rage in the pathogenesis of atherosclerosis, rose to pathologic levels.

DR. DOCK: That is what I would expect from a low protein intake. Theirs is a very low protein intake. The figures of Li and Freeman suggest that when the protein intake goes down, trouble arises in cholesterol metabolism, and one may do more harm than good by bringing the protein intake down. That is why when I suggest a diet to a patient, I do not make it free of meat. I would rather have them take the cholesterol present in lean meat than risk the trouble which may arise from a diet low in protein.

DR. TOLSTOI: Fanconi and Rosenbush in Switzerland described a disastrous experience in diabetic children who were maintained on a low protein diet. At the end of fifteen years about 75 per cent of them had developed vascular lesions, and at the end of twenty-one years very few of them were alive.

DR. DOCK: The figures of Li and Freeman, which were published in the *American Journal of Physiology*, showed clearly that the protein content of the diet is very important in determining how high the blood cholesterol will go. They had dogs on various diets. The serum cholesterol rose to levels of about 600 mg. per cent, a level at which atherosclerosis develops only in those which receive cholesterol, high fat and low protein.

DR. READER: Dr. Foley?

DR. WILLIAM T. FOLEY: We have been on this discussion of artherosclerosis for about fifty minutes and no one has yet brought up the Orient, which is quite a record for a discussion on arteriosclerosis. We have already gotten the diet low in fat, low in cholesterol and now we have gotten it low in protein. This is an appropriate point at which to introduce the Orient where the experiment is carried on with somewhere near a billion people. They are on a diet low in fat, low in cholesterol and low in protein. What we need now are a few facts about the Orientals. Autopsies are rare in the Orient. We have some from Hongkong. There, under British law, all the dead bodies are gathered up and autopsies are performed on from ten to twenty a day. From 100 to 150 a year used to be done at the Peking Union Medical College. There are no accurate statistics. The dead bodies are not accompanied by a history. One can only guess at the age of the bodies in Hongkong. One learns from this material that they had atherosclerosis but not to the advanced degree we see in our people here.

The Oriental material, however, presented us with an opportunity to pursue another phase of the experiment, since the same kind of people who live in Hongkong come to New York, open up laundries and restaurants, and live here for twenty or thirty years. Some of them who die wind up in our morgues. With Dr. Helpern's

assistance we investigated some of these at autopsy. From the standpoint of atherosclerosis they were no different from native Americans. One may take this to indicate that diet is a factor, not only low protein or only low cholesterol. It is hardly necessary to say, of course, that this is no proof for the factor of diet, for many other factors were not excluded, namely, climate, mode of life, type of employment or any number of other factors. Few problems are so difficult to study as arteriosclerosis. We have had a sample of that in our attempt to evaluate treatment in peripheral vascular disease in our Vascular Clinic during the last five years. These cases seemed more favorable for such work than patients with coronary disease for several reasons. We can measure the temperature of the leg, see changes in color, measure pulsations and obtain plethysmographic records. We started with patients who had been observed for a period of at least a year, providing a baseline which indicated whether the disease was stationary, improving or growing worse. In one group we tested choline; in another, inositol; in some with low and in others with high cholesterol diets. In the five-year period we have not yet discovered how these measures influence the course of the arteriosclerosis. It is possible that changes have taken place but that our means for detecting them are not sufficiently sensitive. I think we have one hope in Steiner's experiments with the hypothyroid dogs fed a high cholesterol diet.

DR. READER: I would question whether the hypothyroid dogs would provide the best material for solving the problem of atherosclerosis in humans. Dr. Eder, would you care to comment?

DR. HOWARD EDER: I have examined some of Dr. Gofman's diets. They seem to me so unpleasant that I would imagine one would be willing to look far and wide for a reason to avoid a low cholesterol diet.

From available data one can estimate that about 15 gm. of cholesterol are produced per day in the normal man and that endogenous synthesis increased during a low cholesterol diet. In the light of our present limited knowledge, such rigid restrictions in diet may, therefore, not be justified.

DR. DOCK: But we are still faced with the experimental facts. How can one get away from the results of the experiments on the rabbits? How can one brush aside the experiments on the dogs? Feeding cholesterol makes the difference between the case in which the blood cholesterol rises and atherosclerosis develops, and the case in which neither of these takes place. In every species the exogenous cholesterol is negligible in comparison with the endogenous. All this shows is that exogenous cholesterol is far more important than endogenous cholesterol in the development of atherosclerosis. As several observers have pointed out, that which is produced by the liver may involve a different process from that absorbed from the gastrointestinal tract. Altschule found that cholesterol heated and cooked at temperatures no higher than those at which we ordinarily fry meats are more effective than unheated cholesterol in producing atherosclerosis in rabbits. And so I do not think much is to be gained from attempts to relate exogenous and endogenous cholesterol. In a sense, the question is quite simple. When a rabbit is fed cholesterol, it develops high blood cholesterol and atherosclerosis. Why does it do that? We could well afford laying aside the question of the relation of exogenous to endogenous cholesterol until this problem is solved.

DR. WRIGHT: I think it might be of interest to cite some of Gofman's recent work. In rabbits there is a constant interchange between the cholesterol laid down in the aorta, in the blood and in other tissues. There is a considerable interchange of exogenous and endogenous cholesterol. These workers also point out that they have strains of rabbits which are resistant to the production of atherosclerosis in the aorta from cholesterol even in very large amounts, but they do not answer the question I raised, namely, why are they resistant?

DR. READER: Dr. Kellner, to end on a hopeful note, I wonder if you might express an opinion as to what we can expect from the use of agents that may prevent or reverse the atherosclerotic process. You have been working with these agents in rabbits.

DR. KELLNER: If we are going to rely on the agents I have been working with, I am afraid I cannot end with a very hopeful note. The agents we have used experimentally, the surface-active agents, seem to have an effect on experimental atherosclerosis in the rabbit. But they are certainly far too toxic to be used in human beings. Dr. Charles Wilkins at Bellevue Hospital was courageous enough to try one of the detergents on himself intravenously. He thought that if he could tolerate it he might then be bold enough

to give it to patients. However, after a short trial he found the effects were so unpleasant that he did not feel justified in risking their use in patients. We shall have to wait for less toxic detergents that may prove effective in altering the solubility or the colloidal stability of blood lipids.

As for lipotropic agents such as choline and inositol, all who have worked with them in chicks and dogs in the past few years have found them without effect on blood phospholipids, and without effect on either the development or the resorption of experimental atherosclerosis.

Dr. Wright earlier referred to the observations on estrogenic materials. This is an extremely interesting problem. At the present time we are endeavoring to confirm that observation, Dr. Wright, because if true it may shed light either on the mode of transport of cholesterol or differences in metabolism of cholesterol and other lipids. Thyroid and iodides have been used but the reports are contradictory. One cannot secure a clear statement as to the effect of thyroid on either human or experimental atherosclerosis.

I must admit I am still very dubious about the low cholesterol diet. The geographical evidence Dr. Dock cited is open to a number of objections. As to the evidence from the Orient that Dr. Foley cited, it is always hurled at us in meetings on cholesterol and atherosclerosis—one might ask the question: What is the average life expectancy of the individual in the Orient on low cholesterol diet in contrast to a group of Orientals in this country who eat our diet? There is probably a forty-year difference in life expectancy. At the recent Macy meeting a gentleman from Ceylon pointed out that life expectancy was forty years in Ceylon. The life expectancy in this country is nearly twice as high. I do not believe, therefore, that the dietary evidence at the present time is sufficiently strong to warrant placing any large segment of the population on the kind of rigidly restricted diet that is necessary to insure freedom from cholesterol. Perhaps the most intriguing possibility is the one mentioned recently by Dr. Beck, namely, the surgical anastomosis. Although it does not affect the atherosclerosis and has no effect on the underlying disease, it alleviates and perhaps removes one of the major causes of death in atherosclerosis, namely, coronary sclerosis and myocardial infarction. If the technics are perfected, and if they prove to have the value indicated by Dr. Beck, it may be at the present time about the most promising measure on the horizon for the therapy of atherosclerosis.

SUMMARY

Dr. Harry Gold: The discussion we have just heard supplies abundant proof that the topic of today's conference was a wise choice. Is a low cholesterol diet of any value against atherosclerosis? Will it prevent the process? Will it reverse it? Will it retard its progress?

Briefly, two opposite positions have been indicated: (1) that human atherosclerosis is caused by eating a diet rich in cholesterol, and that this form of vascular degeneration is favorably influenced by cholesterol-free diet; (2) that human atherosclerosis is not brought on by the ingestion of cholesterol, and that cholesterol-free diets offer no promise for the control of the disease. These views are brought into opposition by conflicting results from similar experiments and conflicting interpretations of similar results.

The evidence in support of the opposing points of view is presented in the details of the conference. A few of the more important items may be summarized. The special diet is salt-poor, contains fat-poor animal proteins, and is distasteful. The total blood cholesterol level seems to have lost its position as an index of atherosclerosis. New factors now command attention, namely, cholesterol-phospholipid ratios, cholesterol in the beta-globulin fraction, and increased cholesterol molecules of specific dimensions revealed by the analytical ultracentrifuge. Lipotropic factors have been tested but found ineffectual, and detergent agents studied on animals have proved too toxic in humans. The relation of atherosclerosis and sex, the utility of endocrine medications and the role of reduced total caloric intake in the management of atherosclerosis were scrutinized.

A strong case was made out for general reduction of food intake with a view toward maintaining normal body weight, rather than specific restriction of any dietary factor as a means of controlling atherosclerosis. More than ever before the practicing physician must be armed with the kind of information and attitudes concerning the mechanism of atherosclerosis and the place of cholesterol-free diets such as have been explored in this conference for, by reason of the liberal accounts in the lay press, the physician is placed under considerable pressure for action in such matters long before he is prepared by scientific discoveries.

Clinico-pathologic Conference

Polycystic Disease of the Kidneys with Renal Insufficiency

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, A. D. (No. 146850), was a white married executive, fifty-nine years of age, who entered the Barnes Hospital for the first time on May 12, 1947, complaining of abdominal pain. The family history was of interest in that the patient's mother had died at the age of sixty-three from "kidney trouble." The patient had been troubled with hay fever for some years but had otherwise enjoyed unusually good health prior to the present illness. He had led an active life as a business executive and had indulged in golf and other forms of moderate exercise.

Sixteen years before entry, during a routine physical examination, the patient was found to have a systolic blood pressure of 165 mm. Hg. Four years prior to this examination his blood pressure had been normal and he had been accepted for life insurance. He was asymptomatic, however, until one month before admission when generalized soreness developed in the abdomen which was aggravated by motion and pressure. The distress continued for five or six days and then disappeared. It was followed with frequency of urination. He again consulted his physician who noted that the patient's heart was slightly enlarged. There was a soft systolic murmur at the apex. The blood pressure was 210/108. Masses were palpable bilaterally in the abdomen but were not identified. An electrocardiogram revealed sinus tachycardia, occasional ventricular extrasystoles and left axis deviation. A cholecystogram was negative. An intravenous pyelogram showed poor visualization of both kidneys. The non-protein nitrogen was 45 mg. per cent. Because of the abnormal findings the patient was referred to the Barnes Hospital for further study.

Physical examination at time of entry revealed the temperature to be 37°C., pulse 90, respirations 18 and blood pressure 210/110. The patient appeared well nourished and in no distress. Examination of the eyes revealed early diffuse cataracts. The fundi were notable only in that there was slight arteriolar narrowing. Examination of the upper respiratory tract was negative. The lungs were clear to percussion and auscultation. The heart was slightly enlarged to the left and a few ventricular premature contractions were noted. The sounds were loud but there were no murmurs. Abdominal palpation revealed multiple lobulated masses in each flank. These descended slightly on inspiration and were firm and slightly tender. Neither the liver nor the spleen was felt. The prostate was moderately enlarged. The pulsations in the extremities were of good quality.

The laboratory data were as follows: Blood count: red cells, 4,750,000; hemoglobin, 12.3 gm.; white cells, 6,900; differential count, normal. Urinalysis: specific gravity, 1.009; albumin, 1+; sugar, negative; centrifuged sediment: many red and white blood cells. Stool: guaiac positive. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 42 mg. per cent; total proteins, 6.8 gm. per cent; albumin, 4.2 gm. per cent; globulin, 2.6 gm. per cent. Roentgenograms: An open film of the abdomen showed no demonstrable renal shadows. A soft tissue mass was noted in the upper lateral portion of the left upper quadrant and was thought to represent a spleen of normal size. A large soft tissue mass with well defined lateral and inferior margins was visualized in the left lower abdomen just below the crest of the ileum on a level with the bodies of the third and fourth lumbar vertebrae.

Shortly after entry the patient was subjected to retrograde pyelography; the findings were consistent with a diagnosis of bilateral poly-

cystic kidneys. The patient excreted between 5 and 10 per cent of injected PSP dye in two hours. The renal clearance was 36 per cent of average normal standard. Maximum concentration of the urine observed was 1.012. A urine culture was positive for Staphylococcus albus. The patient's course was uneventful and he was discharged on May 15, 1947.

Following discharge he was followed up carefully. He was advised to reduce his activities and he did quite well until signs of cardiac decompensation developed. He was maintained on digitalis for over a year, but two weeks before entry the medication was discontinued because of the patient's vomiting. During the three-year interval between his first and second admissions he had had at least six episodes of pulmonary edema. His non-protein rose to a level of 72 mg. per cent, and his blood pressure remained at 180/120.

Two months before his second admission the patient became quite ill. Anorexia, nausea, vomiting and weakness developed and he was forced to remain in bed. Local and generalized muscle twitchings became prominent and on October 17, 1950, he was admitted to the Barnes Hospital for the second time.

At the time of physical examination the blood pressure was 190/100. The patient's breath was uremic. He appeared moderately pallid. Bilateral cataracts were present and the fundi revealed arteriolar narrowing and A-V nicking without hemorrhages or exudate. The border of cardiac dullness was 14 cm. from the midsternal line in the sixth left interspace; the apical impulse was forceful. A grade 2 apical systolic murmur and a diastolic gallop rhythm were heard. The multilobulated masses previously palpable in the abdomen were larger than on the first admission. No edema was present. Muscular twitching was prominent but Chvostek and Trousseau signs were negative.

The laboratory findings were as follows: Blood count: red cells, 2,880,000; hemoglobin, 8.4 gm.; white cells, 10,500; differential count: stabs, 2 per cent; segmented forms, 95 per cent; lymphocytes, 3 per cent. Urinalysis: specific gravity, 1.008; albumin, 1+; sugar, negative; centrifuged sediment, many white blood cells. Stool: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 290 mg. per cent; CO_2 combining power, 9.8 mEq./L.; potassium, 7.5 mEq./L.; sodium, 145.9 mEq./L.; calcium, 6.2 mg. per cent; phosphorus, 13.5 mg. per cent; total proteins, 6.6 gm. per cent; albumin, 4.6 gm. per cent; globulin, 2.0 gm. per cent. Electrocardiogram: T waves inverted and S-T segments depressed in leads I, AVL, V5, and V6.

Because of his nausea the patient was unable to take fluid or food by mouth. On admission, therefore, he was given 1,000 cc. of 5 per cent glucose in water followed shortly with 250 cc. of red cell residue. Digitalis therapy was begun. On the second day he seemed improved. He received an additional 250 cc. of red cell residue, 1,500 cc. of glucose in water and 1,000 cc. of $\frac{1}{6}$ molar lactate to which calcium gluconate was added. On the third hospital day uremic frost was noted and muscular twitchings were particularly striking. The gallop rhythm persisted. Repeated examination of the urine showed a specific gravity of 1.010, 1+ albumin and 20 to 25 white blood cells and 10 to 15 red blood cells per high power field; no casts were noted. Because of the persistent, severe nausea the patient was given 2,500 cc. of fluid containing glucose, lactate and calcium; he also received 250 cc. of red cell residue. Following these infusions his urinary output increased, nausea diminished somewhat, the gallop rhythm disappeared and the muscular twitchings subsided. Multifocal premature ventricular contractions of the heart appeared; procaine amide was given intravenously but was effective only temporarily. Quinidine therapy was then begun and the extrasystoles disappeared. On the fourth hospital day the patient's red cell count was 3,460,000, the hemoglobin 10 gm. He remained nauseated, however, and had transient episodes of muscular twitching. The various blood chemical findings during his hospital stay are summarized in Table I which also shows the amounts of sodium chloride, $\frac{1}{6}$ molar sodium lactate and calcium gluconate given the patient.

On the fifth and sixth day the patient did not vomit at all and was somewhat better. By the eighth day the nausea had decreased to the point where the patient was able to take nourishment by mouth. Improvement continued and by the eleventh day he was able to sit up. The gallop rhythm reappeared and a friction rub was heard over the precordium. The patient's general condition, however, continued to be satisfactory and by the fourteenth day he felt quite well. The muscular twitching had decreased markedly, the lungs were clear and there was no edema.

During his hospital stay the patient had received penicillin and streptomycin prophylactically. On the fifteenth hospital day, November 1st, an extensive maculopapular, pruritic eruption developed over the trunk and

DR. MELVIN L. GOLDMAN: In many respects this case is quite typical. One of the foremost signs commonly noted in patients with polycystic kidneys is the presence of bilaterally tender abdominal masses.

TABLE I

Date	Oct. 17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Nov. 1
Hospital day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Non protein nitrogen (mg. %)	213	290	....	250	295	....	275	....	240	....	295	255	....	215	195	165
CO_2 (mEq./L.)	....	9.8	....	16.6	20.2	....	16.6	....	19.9	....	19.8	25.3	....	22.3	21.0	22.6
Cl (mEq./L.)	104	....	....	....	97	....	82	....	87	....	80	79	....	76	73	75
Na (mEq./L.)	....	146	....	....	....	....	131	....	122	....	140	....	....	....	129	132
K (mEq./L.)	....	7.5	....	....	....	....	4.2	....	4.0	....	3.9	....	....	....	3.9	4.3
Ca (mg. %)	....	6.2	....	....	....	....	6.5	....	6.7	....	....	....	....	6.9	....	....
P (mg. %)	....	13.5	....	....	....	....	15.0	....	14.8	....	....	....	....	13.0	....	....
Fluid intake (ml.)	700	1250	3400	2700	2400	2600	2400	2400	2900	3000	3200	3000	3300	3600	3000	....
Urine output (ml.)	....	700	1000	1700	1200	1700	1400	1500	2400	1800	1700	2300	1900	2100	1300	....
$NaCl^-$ (gm.)	....	....	8.5	....	....	....	....	8.5	....	16.5	8.5	....	....	....	12.5	12.5
M/6 Na Lactate (L.)	....	....	1	1	....	....	....	1	....	1	1	....	....	....	1	1
Ca Gluconate (gm.)	....	4	4	4	....	....	....	4	....	4	4	4	....	....	4	4

the drugs were discontinued. In the evening the patient became somewhat disoriented and his muscular twitchings increased. Several hours later pulmonary edema developed which responded temporarily to the usual measures. Shortly thereafter, however, the patient had a generalized convulsion and expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: I believe all of us would agree with the clinical diagnosis of polycystic kidney disease which was made in this case. Despite the fact, therefore, that no diagnostic problem is presented, the case does offer us the opportunity to discuss both this serious disorder and the important syndrome, uremia. Dr. Goldman, will you open the discussion by telling us whether this case is a representative example of polycystic kidney disease.

DR. ALEXANDER: May I interrupt you to ask whether the involvement in polycystic kidney disease is always bilateral? Is the enlargement apt to be symmetric?

DR. M. L. GOLDMAN: The involvement is almost always bilateral but it is not unusual for one of the cystic masses to be more prominent than the other. When enlargement is first noted, it may be limited to only one side. As the course progresses, however, usually both kidneys become palpable.

DR. ALEXANDER: I ask that question because I remember a patient we saw in whom a unilateral mass was felt. The patient had hematuria and a diagnosis of renal tumor was made. The patient was subjected to operation and only then was the correct diagnosis of polycystic kidney disease made.

DR. M. L. GOLDMAN: I believe there are cases in the literature in which one kidney was

actually removed, presumably for unilateral renal disease, only to have contralateral cystic disease become apparent subsequently in the remaining kidney. The diagnosis of polycystic kidney disease is made usually in two different age groups. It is recognized in very young children and in patients in the fourth or fifth decade. Why there is such a long period between the two age groups afflicted is not clear.

DR. ALEXANDER: It was recorded in this patient's history that his mother died of kidney disease. Is polycystic kidney disease a familial affection?

DR. M. L. GOLDMAN: This disease is transmitted by dominant genes and can be passed by either parent. There are a number of instances on record in which the disease has appeared for three or four consecutive generations in one family.

DR. EDWARD MASSIE: I believe Dr. Alfred Goldman followed up a family in whom polycystic kidney disease occurred in several successive generations.

DR. ALFRED GOLDMAN: The family which I have followed up is now in its fifth generation; five members of the fourth generation of this family have the disease. Four of them have already died and in three the diagnosis was substantiated by postmortem examination. The father of these five patients also had polycystic kidneys as did his brother; one of the brother's children, who is a first cousin of the five people in the fourth generation, also is afflicted. The family history has been studied and we have found that the fourth wife of the great-grandfather had the disorder and transmitted it. The progeny of the great-grandfather's three previous marriages have thus been free of the disease. To date, the children in the fifth generation are asymptomatic but they are being observed carefully.

DR. ALEXANDER: Did any of these people have cystic disease in other organs?

DR. A. GOLDMAN: The first patient subjected to postmortem examination was found also to have cystic disease of the liver. In most of the affected members of this family signs or symptoms did not develop until the members were in their third or fourth decade, and many of them lived for a considerable number of years after the onset of albuminuria or other renal signs.

DR. ALEXANDER: The patient under discussion today lived only three years after the disease was discovered. What is the usual course, Dr. Goldman?

DR. M. L. GOLDMAN: The duration of life after onset of symptoms may vary considerably. Thus in one series 45 per cent of the patients lived less than four years after onset of symptoms, 38 per cent from four to ten years and 13 per cent more than ten years. In a very small percentage of patients symptoms may go on for as long as twenty years or more. In regard to the diagnosis of polycystic kidney disease I should like to point out that one may have to rely on pyelograms in order to substantiate the clinical diagnosis, particularly in the early stages.

DR. ALEXANDER: Hypertension often develops in patients with polycystic disease of the kidneys. Would you comment on its pathogenesis?

DR. M. L. GOLDMAN: As you have indicated, Dr. Alexander, although a large number of patients with this disease develop hypertension, not all of them do. Probably the incidence of hypertension is of the order of 60 per cent. It has been postulated that hypertension develops because of reduction in functional renal parenchyma, the reduction being occasioned by the encroachment of cysts. It is thought that pressure of the cysts on the blood vessels of the kidney may be a factor in the development of hypertension. These explanations do not help us understand why hypertension does not develop in 40 per cent of the patients with the disease. Presumably one would have to invoke the concept that the non-hypertensive patients have enough normal renal tissue remaining so that pressor substances or other hypertensive agents are rendered ineffective.

DR. ALEXANDER: It is interesting to recall that this patient was first noted to have hypertension sixteen years before his death. In some respects it may be difficult to attribute hypertension of sixteen years' duration to the polycystic disease since the latter was not discovered until three years before the patient's death. Had there been sufficient cystic involvement to produce hypertension sixteen years previously, one would have expected the diagnosis to become apparent sooner, particularly since the patient had been followed up carefully over the whole period. Furthermore, he was a very busy, dynamic executive in a large firm and one might assume that he was a candidate for essential hypertension *per se*.

DR. M. L. GOLDMAN: I think I would agree with you, Dr. Alexander. It is not likely that the

patient had renal hypertension for sixteen years. It seems very possible that he had so-called neurogenic hypertension which was made worse by the renal involvement incident to progressive polycystic disease.

DR. THOMAS H. HUNTER: Isn't it true, however, that patients with glomerulonephritis may have hypertension for many years before serious renal insufficiency develops? Could not similar mechanisms operate in polycystic kidney disease so that a patient might exhibit hypertension for many years before any other signs of renal involvement became apparent?

DR. M. L. GOLDMAN: In my opinion the two diseases (polycystic disease and glomerulonephritis) are not really comparable, either clinically or otherwise. Polycystic disease is compatible with a course lasting, as we have indicated, thirty to fifty years. Most patients with chronic glomerulonephritis do not enjoy such longevity. Various explanations have been advanced to explain the fact that patients with polycystic disease do live relatively long with serious renal disease. It has been said that because the disease is slow in onset there is consequently adequate time for "adjustment." A second point in this regard has been based on studies performed in two patients with polycystic disease just prior to their death. Inulin was injected intravenously and its concentration in the cystic fluid was determined. It was found that inulin concentration in the cystic fluid was greater than that in the blood, suggesting that water was probably being reabsorbed from the cysts and that there was also filtration into the cysts. How much the cysts contribute to renal function is questionable, but the possibility exists that they may make some contribution.

DR. ALEXANDER: It is stated that patients with polycystic kidney disease rarely exhibit cardiac failure. No explanation for this clinical observation is known. This patient, Dr. Massie, had repeated episodes of pulmonary edema which suggest recurrent left-sided failure. Do you agree that polycystic disease of the kidneys is not usually associated with cardiac failure?

DR. MASSIE: The instances in which I have seen patients with this syndrome exhibit heart failure are somewhat limited; but as far as I can recall, failure was due to associated hypertension and/or coronary artery disease in each case.

DR. ALEXANDER: Dr. Daughaday, just before this patient entered the hospital for the first time his non-protein nitrogen was 42 mg. per cent. About nine months later it had risen to 72 mg. per cent; and when he was admitted for the third time, he had advanced renal failure. His physician, who had followed him up carefully, however, noted that the patient was free of any symptoms of uremia until three months prior to the second admission. Would you discuss the relation of blood non-protein nitrogen levels to the symptomatology of uremia?

DR. WILLIAM H. DAUGHADAY: The non-protein nitrogen measures all of the nitrogenous compounds which exist in the blood and are not removed by protein precipitation. Approximately two-thirds of this material represent urea and the remainder is accounted for by creatinine, uric acid, glutathione, amino acids and a variety of other substances. In uremia, urea is probably the most innocent of all the components of the non-protein nitrogen in regard to the production of uremic symptoms. Guanidine, a toxic substance, accumulates in the blood in uremia and may contribute to some of the central nervous system symptoms. It is interesting that the retention of uric acid in uremia rarely if ever is accompanied by clinical gout. Undoubtedly unrecognized toxic substances accumulate in uremia and are responsible for most of the harmful effects of this metabolic disturbance. It is well known that patients with slowly progressive renal disease may tolerate uremia quite well; but when uremia develops over a short period of time, it is apt to produce a much more alarming clinical picture. Why this particular patient's non-protein nitrogen rose from 90 to a level of 290 mg. per cent in a short space of time is not entirely clear. Actually, though, the rapid accumulation of nitrogenous wastes may have represented the result of a minor change in renal function. A delicate balance existed which kept the non-protein nitrogen at a level of 90 mg. per cent. Once renal function began to deteriorate further, the non-protein nitrogen rose rapidly.

DR. ALEXANDER: The problem presented by this patient in regard to electrolyte balances was indeed a complicated one. For example, the carbon dioxide combining power of the blood was extremely low. Dr. MacBryde, why does acidosis develop in uremia?

DR. CYRIL M. MACBRYDE: One of the most important functions of the kidney is to rid the body of waste products. When kidney function is impaired, its ability to excrete acid and to

form ammonia is decreased or lost. This impairment of functional capacity results in the loss of sodium which, in combination with the retention of organic and inorganic acids, leads to a decrease in the carbon dioxide combining power.

DR. ALEXANDER: In this case lactate was given in an attempt to combat the fall in carbon dioxide combining power. Is it effective therapy under such circumstances?

DR. MACBRYDE: It is often of temporary benefit.

DR. ALEXANDER: This patient also had a serious disturbance in calcium metabolism with a low blood calcium. Why is the calcium low in renal insufficiency, Dr. MacBryde?

DR. MACBRYDE: The hypocalcemia which occurs in uremia is due primarily to retention of phosphate. Calcium and phosphorous exist in a reciprocal relationship; and if phosphate is retained, calcium falls.

DR. ALEXANDER: How effective is calcium gluconate in combating the symptoms of hypocalcemia?

DR. MACBRYDE: It is effective for a short period but never for very long.

DR. HUNTER: Dr. Alexander, could we return to the problem of the relation of the carbon dioxide combining power to the blood calcium level? In this particular case may there not have been overcorrection of the carbon dioxide combining power leading to alkalosis and tetany? Some degree of acidosis is probably beneficial in the presence of hypocalcemia.

DR. MACBRYDE: I think Dr. Hunter's point is a good one. One must exercise care in raising the carbon dioxide combining power in patients with the acidosis of renal insufficiency, for the proportion of ionized calcium is higher in acidosis than it is normally. As Dr. Hunter has pointed out, mild acidosis is indeed a protective mechanism against tetany and convulsions because it increases ionization of calcium.

DR. M. L. GOLDMAN: The problem is complicated, however, by the fact that the kidney may suffer further damage because of acidosis. For that reason, although overcorrection should be avoided, severe acidosis should be corrected.

DR. ALEXANDER: What value for the carbon dioxide combining power is optimal?

DR. M. L. GOLDMAN: I don't think your question can be answered definitively. I would suggest that the carbon dioxide combining power should be kept at levels of the order of 20 mEq./L.

DR. HUNTER: Isn't it important to know what the pH is?

DR. DAUGHADAY: The pH of the serum is really the important factor as far as calcium and phosphorous are concerned, and in chronic uremia one has to be careful about estimating the pH on the basis of the blood bicarbonate. The pH is determined to a considerable extent by the activity of the respiratory center, and the respiratory center probably is not as acute in its adjustment of the rate of ventilation in uremia as it is normally. The situation is similar to that which obtains in diabetic coma where it is well known that following recovery from coma, patients may develop alkalosis with a bicarbonate level below normal. The objective of treatment should be to restore the serum pH to normal, or at least toward normal.

DR. ALEXANDER: Dr. Daughaday, may we ask you why the patient's potassium was so high?

DR. DAUGHADAY: Generally potassium is handled well by the kidney. There has to be tremendous reduction in functional renal tissue before potassium is retained. I believe the retention noted in this case reflected the marked degree of filtration failure which existed, so that the tubules were unable to excrete the excess potassium.

DR. ALEXANDER: It was very difficult for those taking care of this patient to maintain normal chloride values. The serum sodium was likewise low. Would you discuss this particular problem?

DR. DAUGHADAY: In the first place, there is a tendency for hypochloremia in chronic renal disease partly because of the retention of organic acids in the blood. Compensation is based not only on the reduction of bicarbonate, but to some extent also on reduction of chloride. The explanation for hyponatremia probably lies in the fact that the seriously diseased kidney loses its ability to control sodium and water loss. The loss of sodium is relatively greater than that of water. If a patient so affected is given isotonic fluid, adequate restoration of electrolyte balance is impossible. In the absence of edema, therefore, hypertonic sodium solution should be given. When the combination of hyponatremia and edema occurs, one faces as difficult a problem as I know. Our present form of therapy in such a situation, namely, the administration of hypertonic sodium solution, although often

unsatisfactory is given in the hope that with restoration of serum sodium renal function will improve so that the retained fluid can be excreted.

STUDENT: I wonder if Dr. Daughaday would explain the fact that although the patient's non-protein nitrogen decreased moderately from the second to the fourth day and the serum chloride fell only slightly, the carbon dioxide combining power more than doubled. During this period he received only 1 or 2 L. of 1/6 molar lactate.

DR. ALEXANDER: Not shown in Table 1 is the fact that the patient received considerable 5 per cent glucose in water during this period.

DR. DAUGHADAY: I would suspect that adequate hydration improved the patient's renal function sufficiently to lead to some lowering of the non-protein nitrogen. I would agree, however, that the amount of 1/6 molar lactate which the patient received during this period was not sufficient to explain the rise of carbon dioxide combining power.

DR. ALEXANDER: As is characteristic in uremia, this patient had anemia for which he was given red cell residues on several occasions. Dr. Loeb, could you discuss the pathogenesis of the anemia of uremia and also the use of transfusions of red cell residues in therapy?

DR. VIRGIL LOEB, JR.: Three explanations have been offered for the anemia of uremia. The first of these, which is probably the least important, is that of blood loss. When this patient was first seen in 1947, he had a red count of 4,500,000 with only 10 gm. of hemoglobin; he thus exhibited some degree of hypochromia. Many red cells were found in his urine at that time. It is possible, therefore, that the loss of red cells in the urine could have accounted for the slight hypochromic anemia. However, as time went on his hemoglobin and red cell values fell to seriously low levels and the anemia became normocytic in character. Normocytic anemia, of course, cannot be attributed to blood loss. A second explanation advanced has been bone marrow failure, that is, inhibition of bone marrow function by products circulating in the blood stream. In a series of bone marrow studies done by Limarzi[1] on patients with uremia several years ago inconsistent results as far as evidence of bone marrow failure were obtained. No correlation could be made between bone marrow depression and the non-protein nitrogen until the latter had risen to very high levels. More recently a third possibility, namely, a hemolytic factor, has been suggested. The latter possibility is based on evidence that red cell survival in uremia may be shorter than normal, presumably because of the presence of a circulating hemolysin. Thus Dr. Philip Loge, when he was working in these laboratories, showed that in some patients with chronic uremia, even though they exhibited only moderate elevation of the non-protein nitrogen, some degree of hemolysis could be demonstrated.

DR. ALEXANDER: Dr. Moore, when this patient was seen three years before his death, his PSP excretion was only 10 or 15 per cent of normal, the non-protein nitrogen was slightly elevated and the urea clearance was about 32 per cent of normal standard. Would you discuss renal function tests, particularly in terms of desirability, if one suspects renal failure?

DR. CARL V. MOORE: A simple and practical procedure is the determination of the ability of the kidney to concentrate. One of the first evidences of renal failure is the loss of this concentrating power. The urea clearance test, although more expensive and more difficult to do than some of the other tests, is very helpful. PSP excretion is probably the least valuable measurement; when decreased it of course signifies renal failure, but there must be relatively advanced renal impairment before there is a decrease in PSP excretion.

DR. ALEXANDER: Do you believe that intravenous pyelograms are helpful?

DR. MOORE: Yes, I do. During the discussion of PSP excretion I should have mentioned, also, that if retrograde pyelography is done differential excretion of PSP by each kidney may be helpful in indicating whether one kidney is more damaged than the other.

STUDENT: Would parathormone be useful in a situation such as this one to achieve higher serum calcium levels?

DR. MACBRYDE: With the degree of renal impairment this patient exhibited, it is doubtful that parathormone would have been effective. Even in the presence of normal renal function one has to give parathyroid extract regularly in order to prevent tetany in hypocalcemic patients. When renal failure exists, use of the parathyroid extract is usually a futile gesture.

DR. HUNTER: Do you believe that adsorption of phosphates by amphogel or similar substances

[1] CALLEN, I. R. and LIMARZI, L. R. Blood and bone marrow studies in renal disease. *Am. J. Clin. Path.*, 20: 3, 1950.

in the gastrointestinal tract is helpful in the treatment of uremia?

DR. MACBRYDE: I doubt that it helps.

DR. ALEXANDER: In summary, we may say that this patient suffered from polycystic kidney disease with renal failure which developed over a period of three years. At the time of his final admission he presented serious problems in electrolyte balance; and although some measure of success in the therapy of these disturbances was achieved, the patient died in severe uremia.

Clinical Diagnoses: Polycystic kidney disease and uremia.

PATHOLOGIC DISCUSSION

DR. FRED T. CALDWELL, JR.: The lungs were heavy. There was moderate nodularity of all lobes, most marked in the lower ones. The cut surfaces exuded free fluid and on compression purulent material could be expressed from the small bronchioles. The pleural cavities contained small quantities of serous fluid and fibrin. The enlarged heart weighed 600 gm. in contrast to a normal weight of 370 gm. for a man of comparable habitus. The hypertrophy was most advanced of the left ventricular wall. The coronary arteries were only moderately arteriosclerotic. In the myocardium there were small grey areas 5 to 10 mm. in diameter; they were most numerous in the posterior septum. On the surface of the liver there were many 2 to 3 mm. purple cysts that contained clear serous fluid. The kidneys were grossly enlarged and weighing 1,050 and 1,500 gm., respectively. The perirenal fat and capsules were adherent to the surfaces which were covered with cysts varying in diameter from 5 mm. to several centimeters. Most of these cysts contained serous fluid; some contained a brownish material. On section the normal gross architecture was completely obliterated. The lower urinary tract was intact.

DR. GUSTAVE J. DAMMIN: The results of the gross examination confirmed the clinical diagnosis of polycystic kidneys. In addition, other findings included the presence of small cysts in the liver, an enlarged heart, pneumonia and pulmonary edema. Figure 1 shows the microscopic condition of the renal parenchyma as it was found in some portions of the sections. The glomeruli in this region were not in the least unusual, nor were the associated tubular components of those particular nephrons between the several cysts included in this field. Two types of cysts can be found in specimens such as this. In the first one or more glomeruli lie in the wall of the cyst and filter fluid into it. Comprising the second type are purely tubular cysts with epithelium capable of secreting fluid which results in the cyst formation. Figure 2 shows the walls of two adjacent cysts. The lower one was lined by a squamous epithelium, the upper by an almost papillary cuboidal epithelium. In a few cysts from this case a brush border, definitely identifying the epithelium as that of the proximal convoluted tubules, could be discerned. Groups of arterioles in these sections showed hyalinized thickening of the wall, and examples of glomerular changes from thickening of the basement membranes to fibrous obliteration were similar to the changes present in most cases of established hypertension. In other areas (Fig. 3) there was a fair to moderate amount of destruction of renal tubular epithelium associated with slight cellular infiltration around some of the tubules, edema of the parenchyma, necrosis and loss of epithelium and distention of the tubules with a granular precipitated material. These are the changes of so-called lower nephron or hypoxic nephrosis of slight degree, in the phase of recovery.

Figure 4 shows the microscopic character of the cysts on the capsular surface of the liver. Other microscopic cysts of somewhat different configuration were found in the deeper portal structures. (Fig. 5.) They consisted of a network of cystic ducts with a high epithelium and were noted in perhaps half the fields in the microscopic sections. In the pancreas (Fig. 6) there were also microscopic cystic structures although they had not been suspected grossly. The size of the lumens and the thickness of the walls indicate the congenital nature of these cysts in contrast to simply dilated ducts. In Figure 7 the myocardium of the interventricular septum showed a marked increase of connective tissue. Although it was extensive, there was no striking localization of this change, which represented focal fibrosis rather than a healed infarct. The fibrosis was unusually extensive for a heart that was enlarged and as free of vascular sclerosis as was this one. The pneumonia (Fig. 8) was characterized by ulceration of the bronchiolar epithelium and an intense cellular response associated with some destruction of alveolar walls. It represented an early necrotizing bronchopneumonia which was progressing rapidly.

The acute tubular changes in the kidney were compatible with an alteration which could have occurred a week or ten days before death. The record states that there was so much nausea that

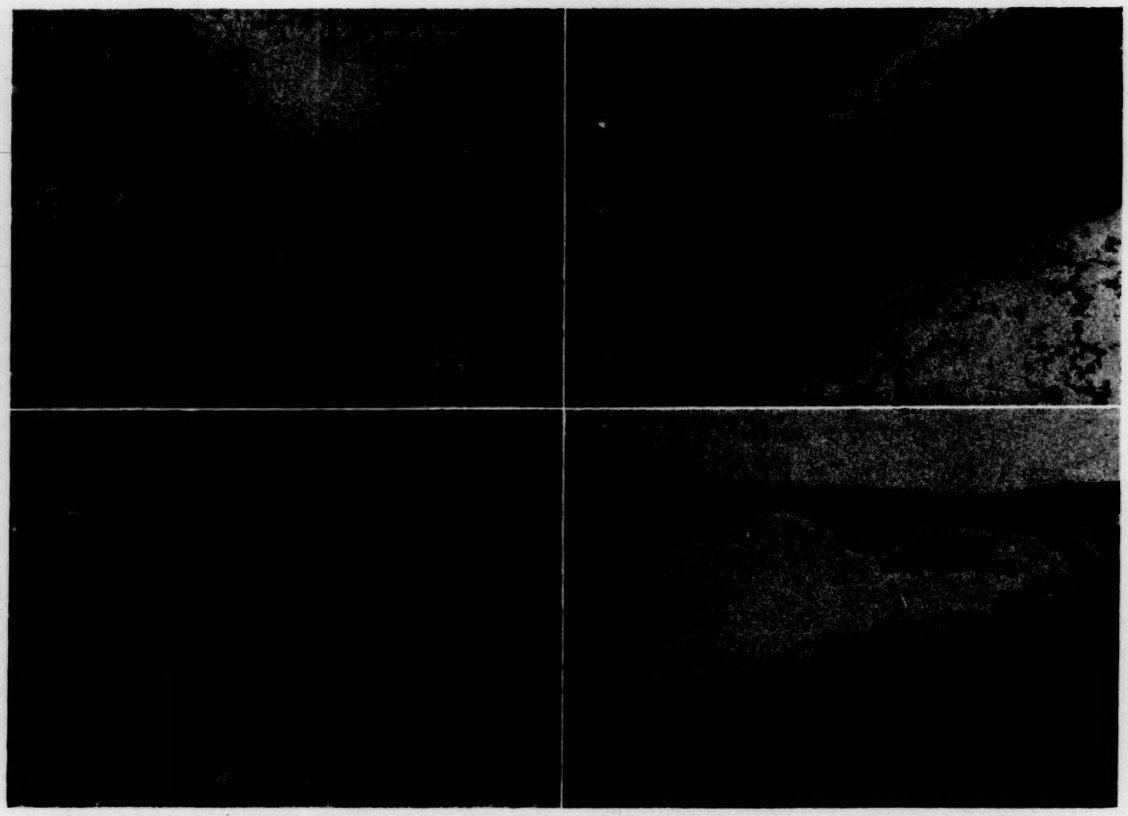

FIG. 1. Kidney in polycystic disease with an island of well preserved renal tissue between several cysts.
FIG. 2. Detail of the walls of adjacent cysts illustrating the two types of epithelial linings found.
FIG. 3. An area of interstitial edema and necrotic changes in the tubular epithelium indicative of a slight and subsiding hypoxic nephrosis.
FIG. 4. Subcapsular cyst in the liver.

the patient could take nothing by mouth for two weeks before admission. There was also severe vomiting and probably some degree of dehydration. Simple dehydration, either from vomiting or acute diarrhea, could have been responsible for the acute renal lesion; however, the record of the urinary output suggested that the lesion was minimal. The only time there was any reduction in output of possible significance was during the second hospital day.

A word should be said about present ideas of the pathogenesis of the cystic lesions observed in the kidney, liver and pancreas, and of similar cysts that are occasionally observed in the lung. Apparently the developmental basis is the same in all these sites. In the normal embryologic development of the ductal systems of these organs an excess of tubular epithelial elements is formed. These provisional elements normally degenerate and disappear. Segmentation of the completely formed epithelial tubules is the first stage of this degeneration, and cystic disease develops when these segments become isolated and fail to regress. They are expanded into cysts by the secretions of their epithelial linings or in the case of the kidney by glomerular filtration into some of the segments formed from the most proximal portions of the tubules. This relatively recently developed concept is an explanation of the polycystic phenomenon in any of these sites in contrast to the older theory that explained the lesion in the kidney as due to failure of union between the anlage of the metanephros and the ureteral bud, and offered no explanation of the coexisting lesions in other organs.[2-4] The older theory was also weakened by the observation

[2] NORRIS, R. F. and HERMAN, L. Pathogenesis of polycystic kidneys. *J. Urol.*, 46: 147–176, 1941.

[3] MCKENNA, C. M. and KAMPMEIER, O. F. Consideration of development of polycystic kidney. *J. Urol.*, 32: 37–43, 1934.

[4] NORRIS, R. F. and TYSON, R. M. Pathogenesis of congenital polycystic lung and its correlation with polycystic disease of epithelial organs. *Am. J. Path.*, 23: 1075–1097, 1947.

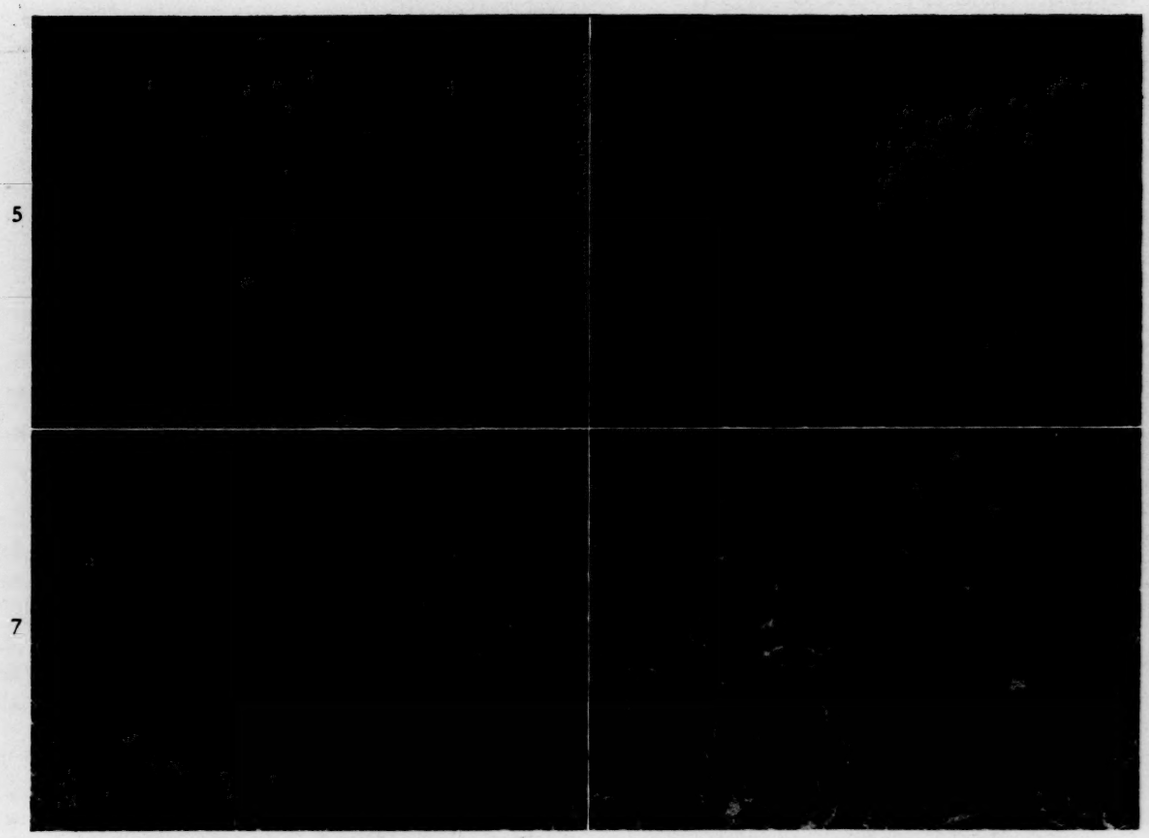

FIG. 5. Cystic dilatation and duplication of bile ducts found microscopically throughout the liver.
FIG. 6. A deformity in the ducts of the pancreas comparable to the two types of cysts illustrated from the liver.
FIG. 7. Widespread focal fibrosis of the myocardium that occurred without significant arteriosclerosis of the coronary arteries.
FIG. 8. Early necrotizing bronchopneumonia that was a terminal event.

that the glomerulus does not develop until and unless the complete tubular nephron is formed. In the development of the kidney apparently four or five generations of fully formed nephrons appear and regress before the definitive set persists, so the opportunity for this organ to be most commonly and most extensively affected is obvious. The coincidence of polycystic changes in other organs in cases of polycystic renal disease, however, is not generally appreciated. In one series of 200 cases the liver was also affected in 30 per cent of instances although the hepatic cysts never had any effect on function.

In the present case the precipitating cause of the terminal episode was not clear. The hypoxic nephrosis, for reasons that have been given, did not seem to have initiated the failure. In other cases the terminal event can result from hemorrhage into a large cyst and occasionally pyelonephritis is recognized as the terminal event. It is interesting that although this patient had reached the age of sixty-three with this lesion and was obviously in renal failure there were still glomeruli which, so far as we could tell, were entirely normal. The arteriolosclerosis which was apparent in the kidney was not necessarily related to the polycystic process. With the long history of hypertension it may well have been due to the independent development of hypertension and arteriolar change. Finally, bronchopneumonia was the immediate terminal factor in this patient's death.

Final Anatomic Diagnoses: Polycystic disease of the kidneys, liver and pancreas; arteriolosclerosis and arteriosclerosis; hypertrophy and dilatation of the heart; subacute hypoxic nephrosis; bronchopneumonia in the lower lobes.

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Case Report

Treatment of Unresolved Pneumonia with Streptokinase and Streptodornase*

JOSEPH J. MUENSTER, M.D., I. J. FLANCE, M.D. *and* BERNARD SWEENEY, M.D.
St. Louis, Missouri

THE two enzymes elaborated by the hemolytic streptococcus, streptococcal fibrinolysin (streptokinase) and streptococcal desoxyribonuclease (streptodornase), have been demonstrated to exert a liquefying effect on serofibrinous, sanguineous and purulent fluids. Clinical trial of these substances by Tillett and his co-workers has been confined largely to pleural exudates, empyema and hemothorax.[1,2] Streptokinase and streptodornase have been used to a limited extent in other local infections such as paranasal sinusitis, sinus tracts due to osteomyelitis and chronic, infected skin ulcerations.[1] The present report relates to the effect of streptokinase and streptodornase, instilled endobronchially, in a patient with "unresolved pneumonia." The use of the streptococcal enzymes in this particular disease syndrome and instillation by this route have not been previously described.

CASE REPORT

The patient was a seventy-five year old white woman who was admitted to the St. Louis City Hospital with the complaints of shortness of breath, fever, chills, cough and pain in the left side of her chest exaggerated by respiration and coughing. These symptoms had been present for approximately five days. The patient had sustained an intertrochanteric fracture about a year prior to her present illness. Several attempts to nail the hip had been unsuccessful. Because of non-union the hip was painful and caused the patient to lie on her left side.

Physical examination revealed an acutely ill patient whose temperature was 102°F. Respirations were rapid (26 per minute) and somewhat labored. Her state of nutrition was fair but dehydration was moderately severe. The thorax was asymmetric, the left side appearing to be somewhat collapsed. Expansion on the left was minimal. There was dullness to percussion over the entire lower one-half of the left chest. Tactile fremitus was absent, voice transmission was poor and breath sounds were decreased to absent in this area.

A roentgenogram of the chest revealed the mediastinum to be shifted toward the left side. There was dense consolidation involving the left lower lobe and possibly the lowermost portion of the left upper lobe. The intercostal spaces on the left side were narrower than those on the right. The clinical diagnosis was pneumonia with atelectasis of the left lower lobe.

Laboratory studies on admission included a urinalysis which showed numerous red blood cells in the sediment. The red blood cell count was 2.94 million per cu. ml. with a hemoglobin of 10 gms. per cent. The white blood cell count was 7,800 per cu. ml.; the differential count showed 5 myelocytes, 12 juveniles, 8 stab forms, 63 polymorphonuclear cells, 11 lymphocytes and 1 monocyte. The blood urea nitrogen was 72 mg. per cent and the blood chlorides 101 mEq. Sputum inoculated intraperitoneally into a mouse killed the animal in less than twenty-four hours and Diplococcus pneumoniae group C was recovered. This organism was cultured from the patient's blood. No acid-fast bacilli were found in six specimens of concentrated sputum, and guinea pig inoculation was negative. No malignant cells could be demonstrated in smears of the sputum.

The patient was hydrated, given a whole blood transfusion and treated with crystalline penicillin, 100,000 units every three hours. Her temperature became normal in approximately thirty-six hours. On the second hospital day bronchoscopy was performed. The bronchial mucosa was found to be edematous and red. Thick purulent material was seen in the left

* From the Unit I (Washington University) Medical Service, St. Louis City Hospital, and the Department of Internal Medicine, Washington University School of Medicine, St. Louis, Mo.

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FIG. 1. Roentgenogram made one day prior to the first instillation of streptokinase and streptodornase. The radiologic findings had remained essentially unchanged during the four weeks of intensive therapy with penicillin and repeated bronchoscopy.

FIG. 2. Roentgenogram made ten days after the first instillation of streptokinase and streptodornase. Note marked clearing of the pneumonic lesion.

lower lobe bronchus and a large quantity was removed by suction. There was no change in the physical findings after the first bronchoscopy. Roentgenographic examination showed slight clearing of the density in the left lower chest. Bronchoscopy was repeated on the fourth and sixth hospital days, yielding lesser amounts of purulent material on each occasion. On the day following the third bronchoscopy breath sounds were heard in the affected area and an x-ray of the chest showed re-expansion of the left lower lobe with pneumonic infiltration remaining. Throughout the course of her illness both prior to and following admission to the hospital the patient had produced no significant amount of sputum. Serial x-ray examinations during the following three weeks failed to demonstrate any noticeable change in the radiographic appearance of the lungs, and physical examination continued to disclose fine crepitant rales. The patient had received 800,000 units of penicillin daily during this entire period.

One month after admission bronchoscopic examination was again performed. The edema and injection of the mucosa previously noted had subsided and no purulence was seen in any of the bronchi visualized. (Fig. 1.) The bronchoscope was directed into the bronchus of the left lower lobe and 20,000 units of streptokinase and 9,500 units of streptodornase in a volume of 5 cc. of saline solution were instilled into the several secondary bronchi of the left lower lobe. The patient tolerated the procedure well and there was no coughing immediately following the instillation. She was made to lie on her left side following the procedure so as to keep the affected part of the lung in a dependent position. Beginning approximately four hours after the administration of the drug and continuing for about eight hours thereafter she coughed up progressively increasing amounts of thin, colorless sputum. The total amount was not measured because of the patient's inability to cooperate. Rectal temperatures taken every two hours remained normal and no systemic effects were noted. Bronchoscopy done on the following day revealed no change in the bronchial mucosa; a small amount of clear, thin fluid was aspirated from the left lower lobe bronchus. A second instillation of 50,000 units of streptokinase and 19,000 units of streptodornase produced results identical with those of the day previous except that there was an elevation of temperature from

98.6° to 100°F. approximately six hours after the drug was given. The patient had no complaints. Physical findings on the following day revealed a striking improvement in the transmission of breath sounds and a marked decrease in the number of rales heard in the affected area. The chest x-ray showed noticeable clearing on the third post-treatment day and further resolution on the seventh post-treatment day. Serial films during the following three weeks revealed progressive clearing and disappearance of all abnormal physical findings. (Fig. 2.) The patient was discharged from the hospital three weeks after treatment. When seen two weeks later she had no complaints, there were no abnormal physical findings and x-ray of the chest showed the lung fields to be clear.

COMMENTS

The dramatic effect of streptokinase and streptodornase on purulent, serous and sanguineous fluids has been clearly demonstrated by Tillett and Sherry.[2] In twenty-three cases of acute fibrinous pleurisy, bacterial empyema and hemothorax treated with the enzymes the fluids drawn from the pleural space were transformed from thick, viscous exudates to thin, freely flowing liquids easily aspirated by thoracentesis. Chemical studies made on the fluids before and after administration of the enzymes showed a rapid rise in the non-protein nitrogen content and a marked fall in fibrinogen content. According to Christensen,[3] and Christensen and McLeod[4] streptokinase liquefies fibrin by activating plasmin, a proteolytic enzyme of human serum. The same authors demonstrated that streptodornase causes depolymerization of the desoxynucleoprotein which is present in high concentration in purulent exudates.

In the case described in this report the enzymes appeared to liquefy the fibrinopurulent material occluding the smaller bronchi of the left lower lobe, thus permitting obstructed segments to drain and re-expand.

The doses of enzymes used amounted to only about one-tenth and one-quarter of the usual intrapleural dose. Although no untoward reactions were noted in the present case, it is possible that larger endobronchial doses may prove to be harmful.

SUMMARY

1. A case of unresolved pneumonia was treated by endobronchial instillation of streptokinase and streptodornase.*

2. The enzymes appeared to hasten resolution by liquefying fibrinopurulent material within the bronchi of the involved lung.

3. The doses used were small and caused no untoward effect either locally or systemically.

4. Further trial of this form of therapy would appear to be indicated in cases of unresolved pneumonia which fail to respond to conventional treatment.

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* The streptokinase and streptodornase was supplied by the Lederle Laboratories Division, American Cyanamid Co., New York, N. Y.

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References: Angiology, (Feb.) 1952 . . . 1. Winsor, T. and Humphreys, P., p.1. 2. Perlman, A., p.16. 3. Samuels, S. S. and Padernacht, E. D., p.20.

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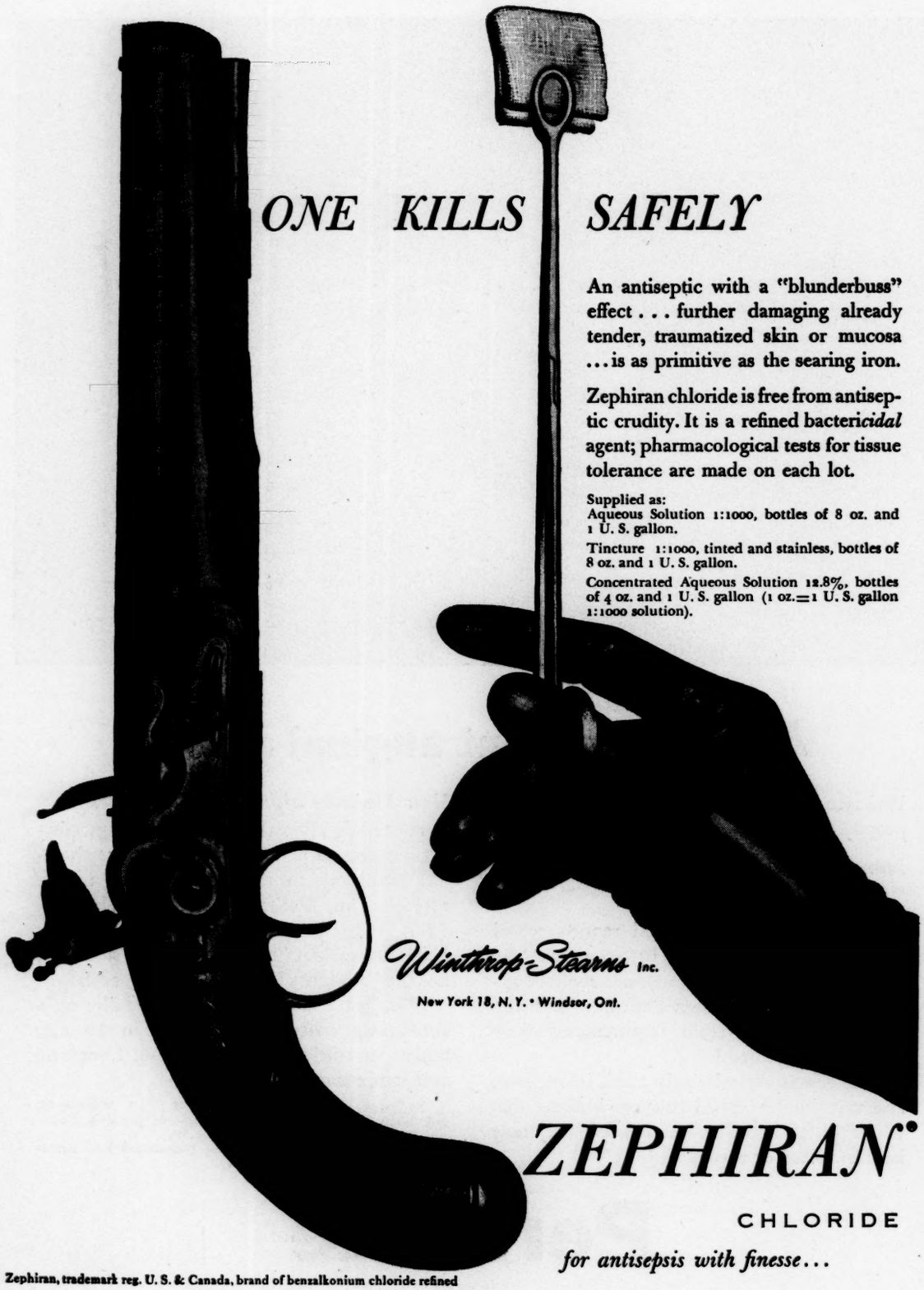

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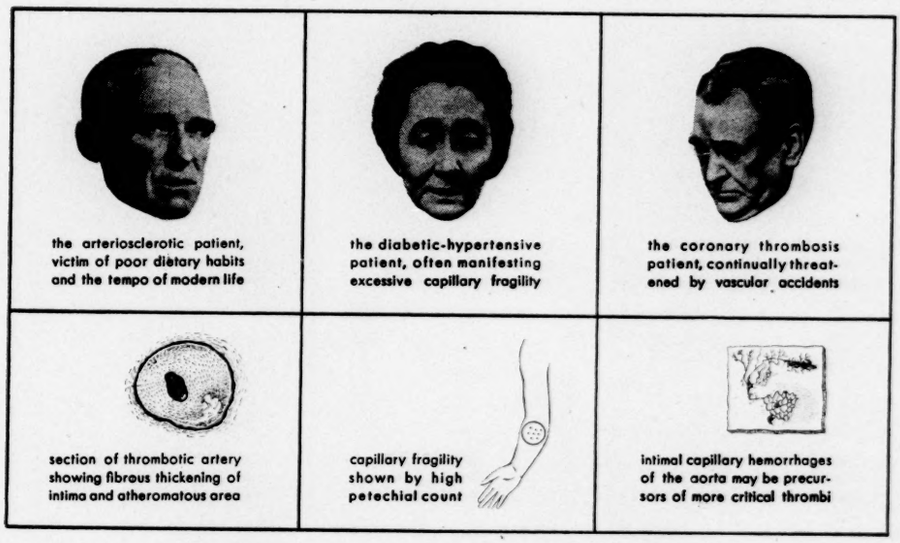

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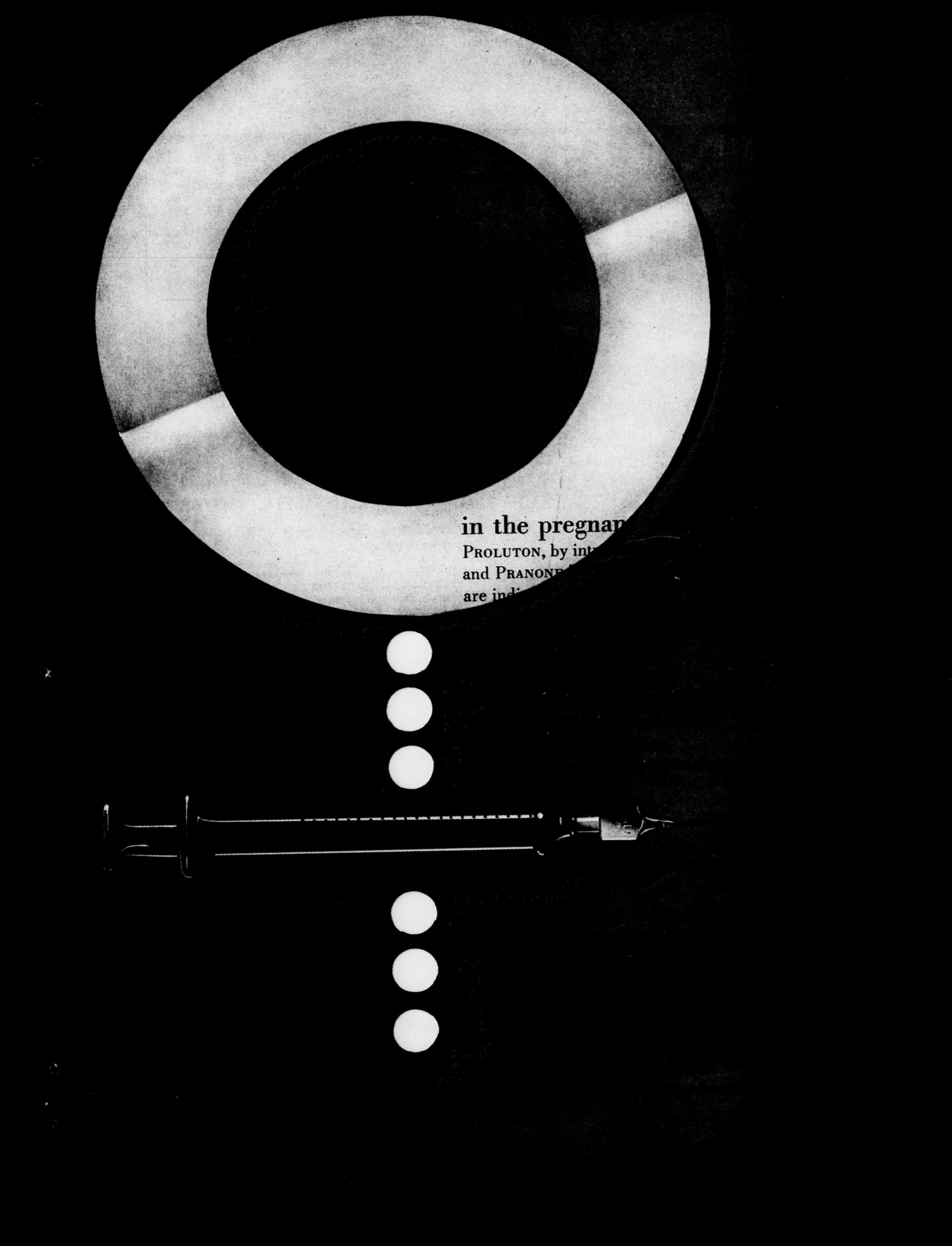
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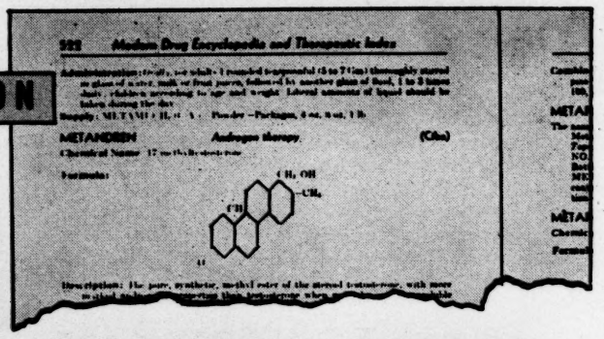

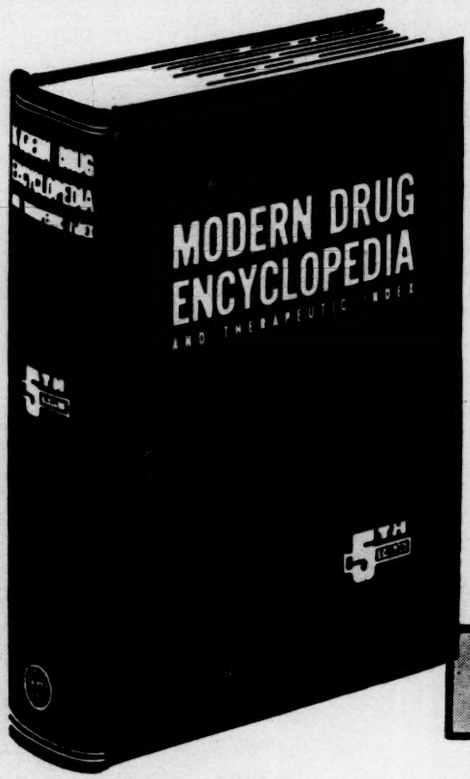

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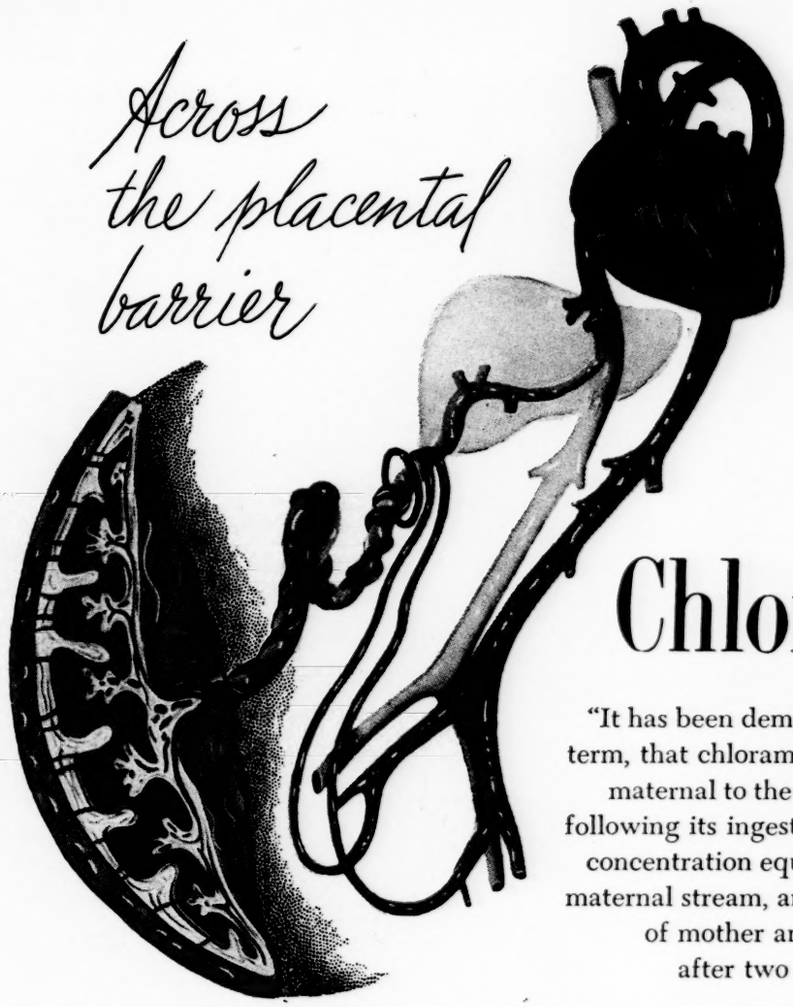

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Bibliography: (1) Stevenson, C. S.; Glazko, A. J.; Gillespie, E. C., and Maunder, J. B.: J.A.M.A. *146*:1190 (July 28) 1951. (2) Scott, W. C., and Warner, R. F.: J.A.M.A. *142*:1331 (April 29) 1950. (3) Ross, S., and others: J.A.M.A. *142*:1361 (April 29) 1950.

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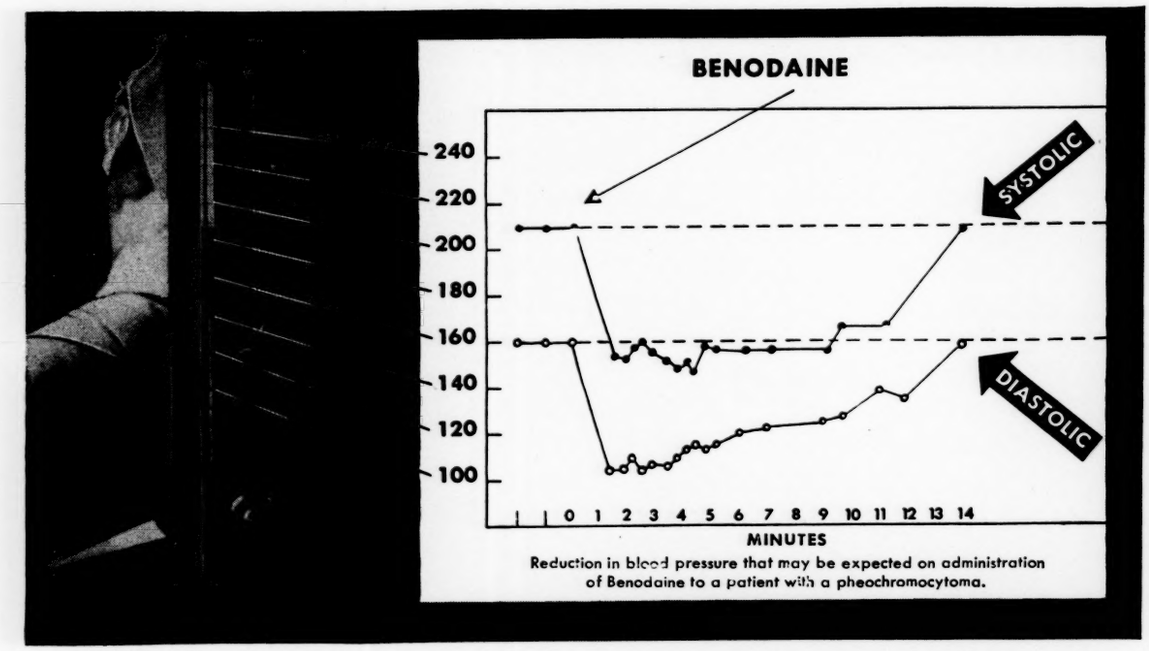

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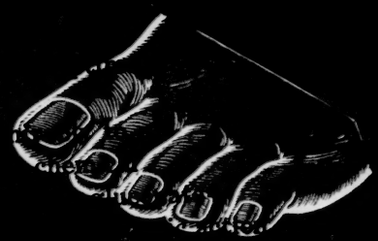

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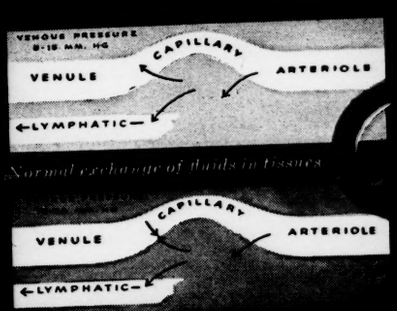

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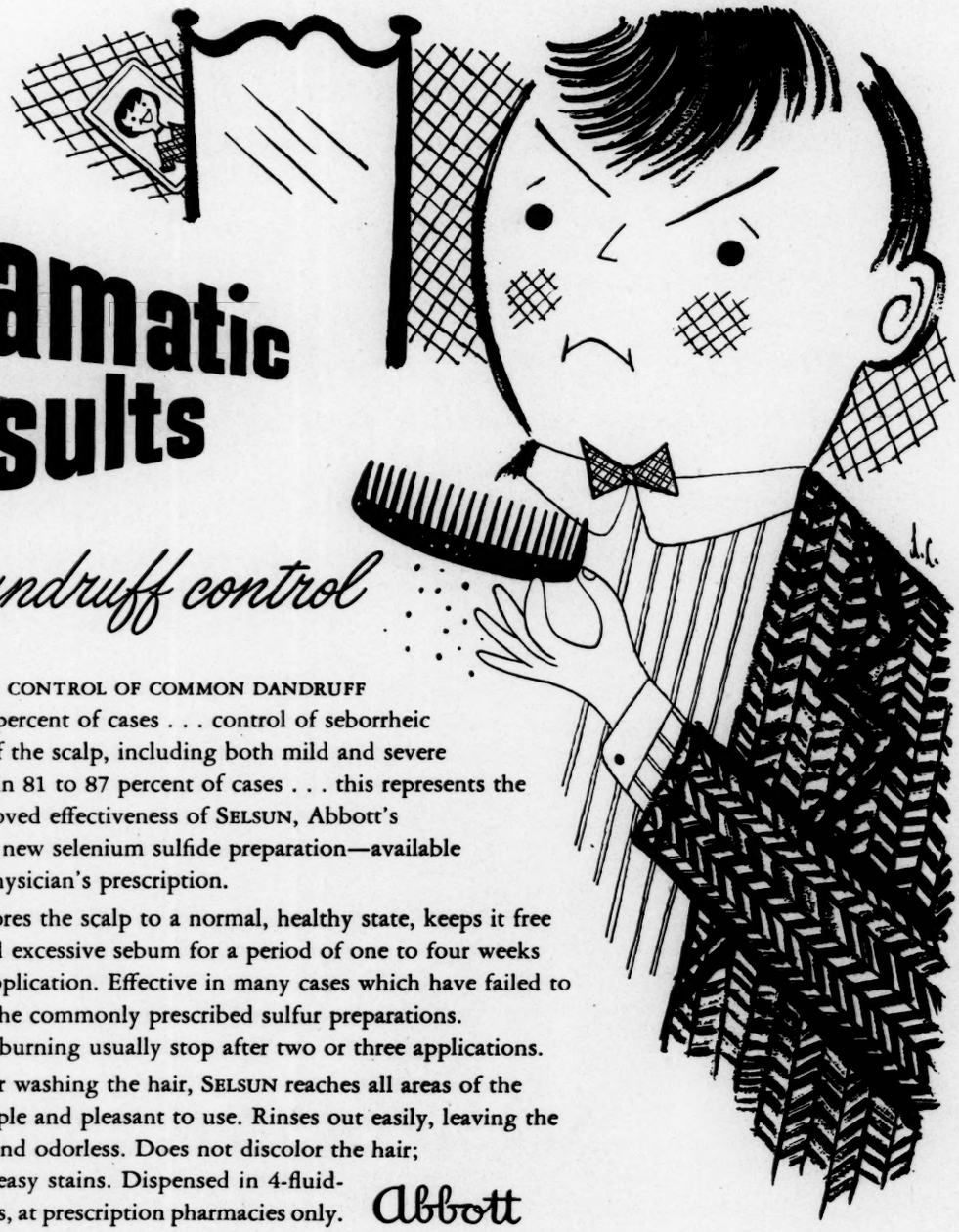

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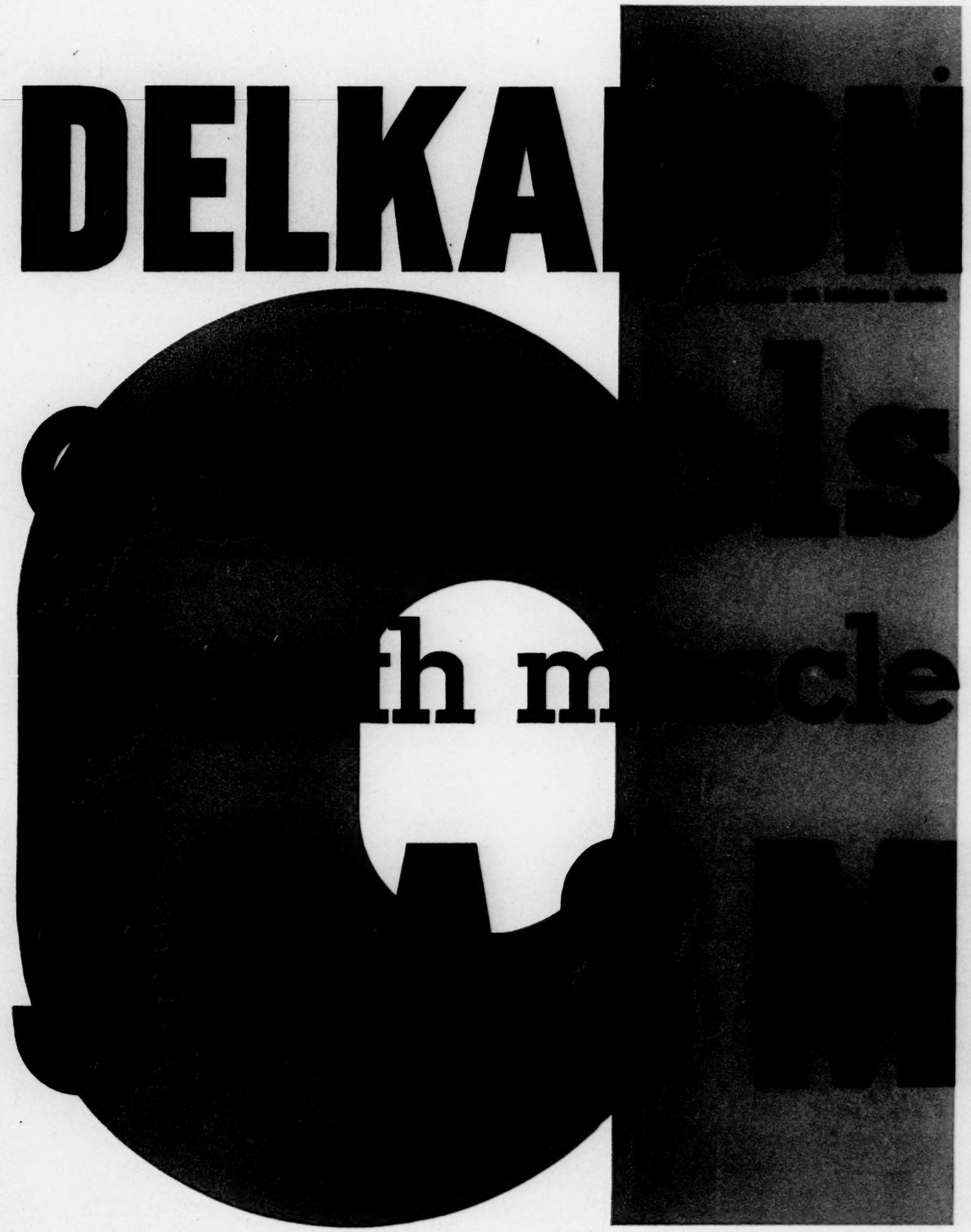

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1. American Practitioner and Digest of Treatment, 1:964, 1947. 2. J. Pharmacol. & Exper. Therap., 87:24, 1946. 3. Ibid., 75:69, 1942. 4. J. Pharmacol. 77:324, 1943. 5. J. Lab. & Clin. Med., 28:405, 1943.

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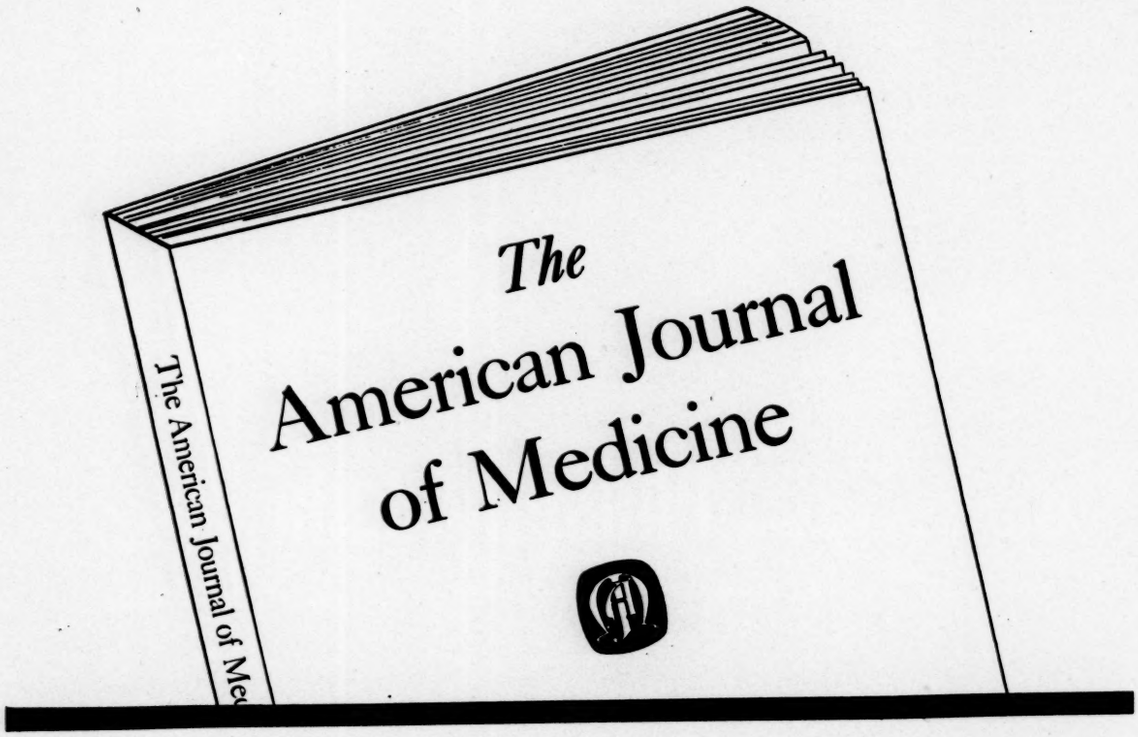

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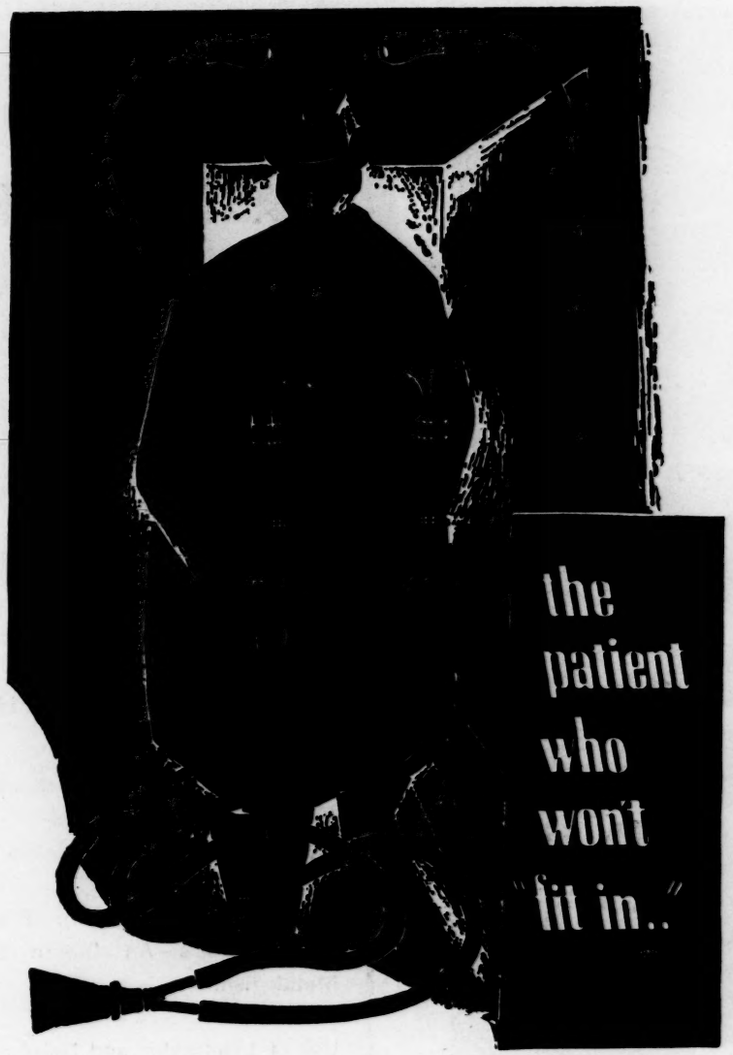

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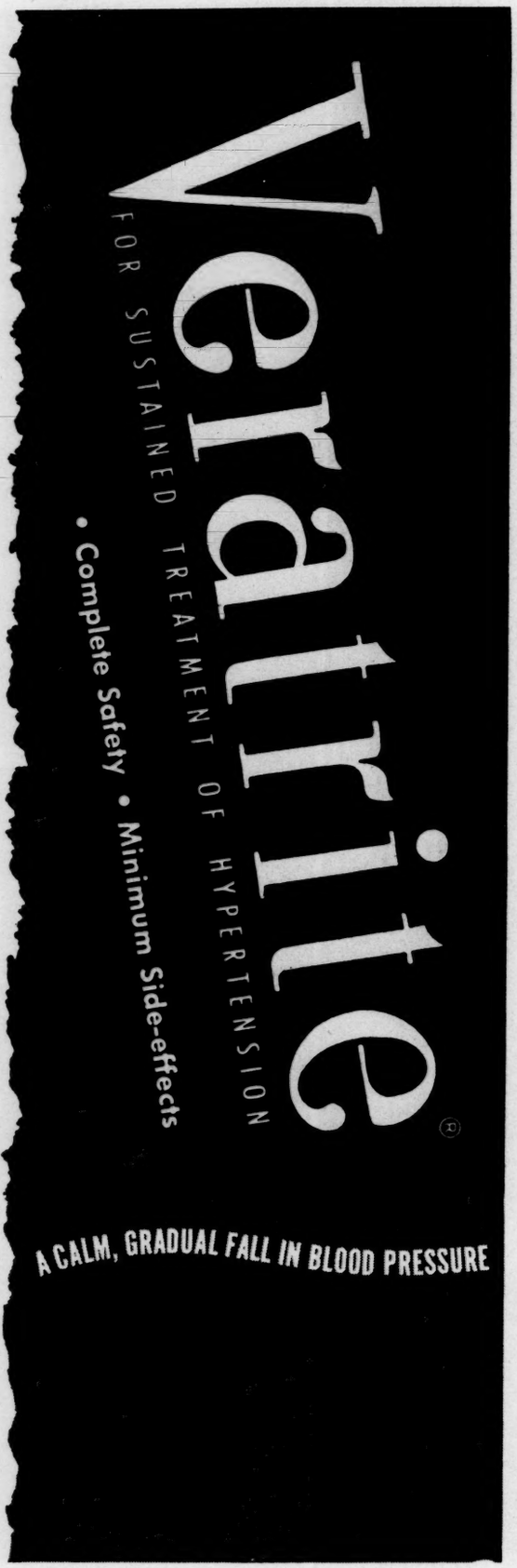
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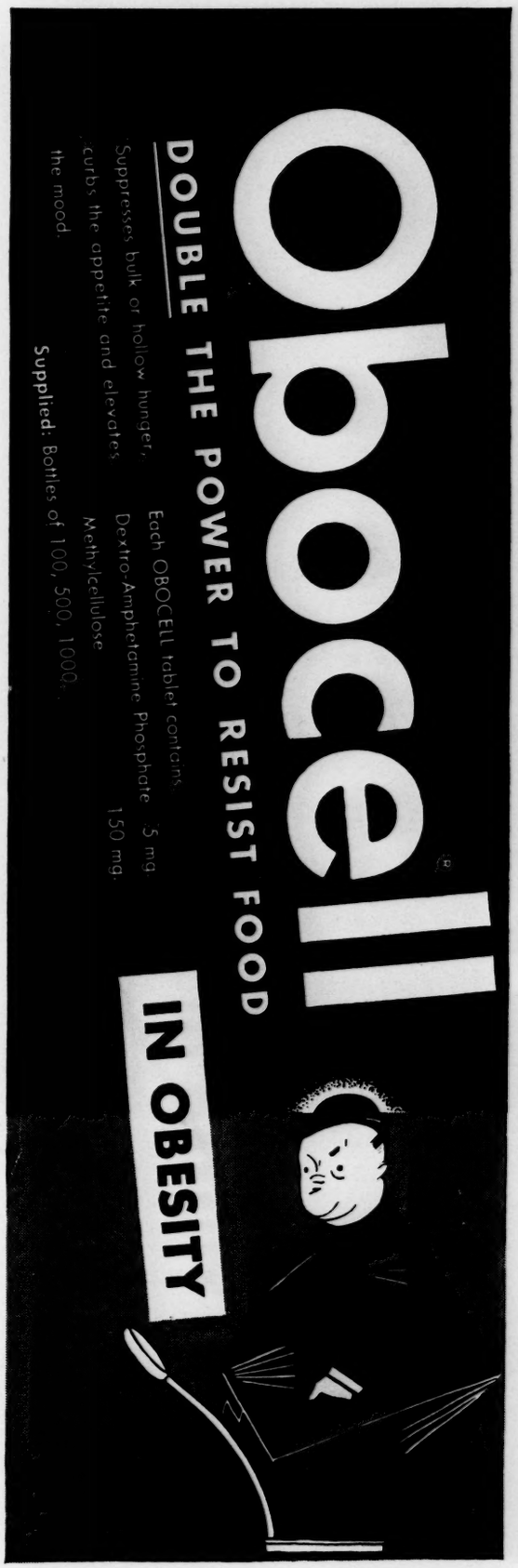

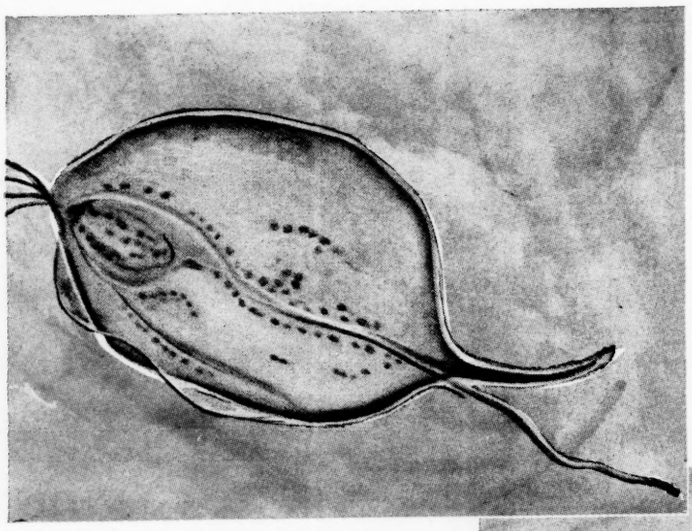

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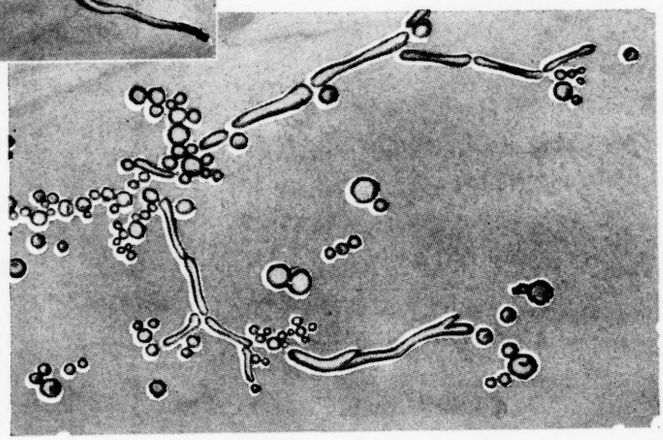

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*Kuder, K.: Vaginal Infections, J. Am. M. Women's A. 5:173 (May) 1950.

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